Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: current situation and future challenges

Lucien Noens,[1] Marja Hensen,[2] Izabela Kucmin-Bemelmans,[2] Christina Lofgren,[3] Isabelle Gilloteau,[4] and Bernard Vrijens[5,6]

[1]Universitair Ziekenhuis Gent, Belgium; [2]Pharmerit BV, Rotterdam, The Netherlands; [3]Bristol-Myers Squibb, Paris, France; [4]Bristol-Myers Squibb, Princeton, USA; [5]MWV Healthcare, Sion, Switzerland; and [6]University of Liège, Liège, Belgium

ABSTRACT

BCR-ABL inhibitors for treating chronic myeloid leukemia in chronic phase have transformed a previously incurable malignancy into a manageable condition. However, suboptimal medication adherence has been observed with these agents affecting clinical outcomes and healthcare costs. In order to raise awareness of the problem of adherence, and before developing pragmatic strategies to enhance medication adherence, a deep understanding of the best approaches for measuring adherence in chronic myeloid leukemia patients and identifying non-adherence is required. A systematic literature review on the prevalence, measurement methods, consequences and risk factors for non-adherence to BCR-ABL inhibitors and adherence-enhancing interventions was performed and critically appraised. Of the 19 included articles, 9 were retrospective. Average adherence varied from 19% to almost 100% of the proportion of prescribed drug taken, but it was measured through various different methods and within different study groups. Suboptimal adherence was associated with a negative impact on both clinical and economic outcomes. There is a lack of supportive evidence demonstrating a difference in adherence across BCR-ABL inhibitors and even contradictory results between the 2nd generation inhibitors. Drug-related adverse events and forgetfulness were common reasons for intentional and unintentional non-adherence, respectively, but further research is required to identify additional reasons behind non-adherence or patients at risk of non-adherence. Non-adherence in chronic myeloid leukemia patients treated with BCR-ABL inhibitors is common and associated with critical outcomes. However, this review highlights important existing gaps, reveals inconsistent definitions, and a lack of standardized methods for measuring adherence in chronic myeloid leukemia. All require further investigation.

Introduction

Chronic myeloid leukemia (CML) accounts for approximately 15% of adult leukemia cases, with an annual incidence of between 1 and 2 cases per 100,000 persons.[1,2] The course of CML is bi- or triphasic; the initial, chronic phase (CP) is asymptomatic in approximately 40% of cases, but can be followed by an advanced accelerated phase (AP) and/or a blast crisis phase, which may prove fatal.[3] CML is a hematopoietic malignancy whose pathophysiology depends upon the presence of the oncoprotein BCR-ABL.[4]

Current treatment has evolved over the years and usually involves the use of oral BCR-ABL inhibitors.[2,5] Imatinib was the first such agent to be introduced as first-line therapy.[6] Newer agents have emerged, namely dasatinib and nilotinib,[7,8] which are associated with higher efficacy compared with imatinib, and acceptable tolerability in patients with newly diagnosed CML-CP.[9-12]

The introduction of BCR-ABL inhibitors has greatly increased the life expectancy for patients with CML and has transformed this disease from an incurable malignancy to a manageable chronic condition. Current guidelines and recommendations state that patients with adequate response to BCR-ABL inhibitors (in the absence of intolerance) should be continued indefinitely on the established treatment.[2,5]

Suboptimal adherence is a serious issue in the management of chronic conditions. Multiple studies across various chronic conditions and therapies, including human immunodeficiency virus (HIV) infection, hypertension or depression, have shown that suboptimal therapy adherence is common and clearly contributes to worse clinical outcomes for patients.[13] According to recent prospective clinical trials, this is also the case in CML.[14,15]

The objective of this systematic literature review is to: i) quantify non-adherence to BCR-ABL inhibitor therapy and its consequences on clinical and economic outcomes; and ii) address definitions and methods used to evaluate adherence in CML, identify predictors of non-adherence and potential patient populations at risk of non-adherence, identify potential adherence differences across treatments, and review existing adherence-enhancing interventions.

A quality assessment of the included papers is performed to help establish the reliability and generalizability of the study findings. The analysis also provides an opportunity to identify additional gaps in research in the literature.

Methods

A systematic review of the literature was conducted to identify all studies reporting on adherence with BCR-ABL inhibitor treatment for CML. The review complies with the Preferred Reporting Items for Systematic Reviews and Meta-

 doi:10.3324/haematol.2012.082511
The online version of this paper paper contains a Supplementary Appendix.
Manuscript received on March 6, 2013. Manuscript accepted on October 30, 2013.
Correspondence: Lucien.Noens@uzgent.be

Analyses statement for systematic reviews.[16] Publication database (EMBASE, PubMed, and Cochrane Library) specific search terms consisted of both single and MeSH terms for the disease, adherence and BCR-ABL inhibitor therapy (*Online Supplementary Table S1*). The last search was conducted on December 20th, 2011. Full-text references were provided for the eligible abstracts that were published after completion of the search process and the analyses. In addition, and due to the lack of existing evidence of adherence in CML, clinical and economic conference proceedings were also searched with a time limit of three years. Preliminary inclusion (or exclusion) of a specific study or conference abstract was based on review of the title and abstract by 2 independent reviewers against pre-specified criteria (Table 1). Final inclusion of the study was based on an in-depth review of the full manuscript. Multiple variables were extracted from the articles to answer study objectives (*Online Supplementary Table S2*). The analysis was descriptive only. Since abstracts in conference proceedings may only provide limited information, and further, due to disparities between data presented in an abstract and those included in a final report/peer reviewed publication, data considered in the present analyses consisted of those extracted from peer-reviewed articles only; information from other retrieved conference abstracts were used within the Discussion section when considered relevant to the analysis carried out.

Overall and individual risk of bias assessments were undertaken on the included peer-reviewed publications to assess study quality.[17] The description of study population, assessment of adherence measurement, type of study analyses and any study limitation were specifically considered. In line with Cochrane guidelines, no formal scoring system was used.[17]

Gaps in the existing literature on adherence were identified and research questions that could not be addressed by the literature review were discussed according to expert opinion during a full-day discussion with European CML practitioners and adherence methodologists (advisory committee), and presented in this study report as add-on information.

Table 1. Inclusion and exclusion criteria.

Topic	Inclusion criteria	Exclusion criteria
Study design	All including reviews (except pharmacokinetic studies, phase I trials, animal studies, *in vivo/in vitro* studies)	Pharmacokinetic studies, phase I trials, animal studies, *in vivo/in vitro* studies
Treatments	BCR-ABL inhibitors: imatinib, dasatinib or nilotinib	Studies on other treatments than BCR-ABL inhibitors
Populations	Patients with BCR-ABL positive CML, treated by selected treatments above	Healthy subjects or patients without CML
Outcomes	Any	Adherence to drug therapy for conditions other than BCR-ABL positive CML
Reporting type	All published studies for which full text is available for manuscripts, or abstract for conference events	Studies for which no full text is available (for manuscripts), or no abstract (for conference proceedings)
Adherence	All studies reporting adherence or compliance (any definition, except persistence or discontinuation[a]), outcomes, measures or predictors	Studies reporting persistence or discontinuation/stop of the CML treatment, also studies reporting reintroduction of CML treatment after discontinuation. Studies only mentioning adherence, but not reporting adherence outcomes, measures, or predictors

CML: chronic myeloid leukemia. [a]The review did not investigate the effect of treatment discontinuation other than issues of adherence, e.g. ongoing trials assessing a potential cure of the disease after stopping treatment once the patient responds to treatment were excluded.

Results

Literature search

In total, 318 articles and 25 abstracts were identified. After checking for duplicates between databases (n=67) and applying the inclusion and exclusion criteria (237 studies were excluded), a final total of 39 studies (19 articles and 20 abstracts) were included in the review (Figure 1). An overview of the included articles is given in *Online Supplementary Table S3*.[14,15,18-54] Only 19 peer review articles were analyzed and reported in the Results section.

Eight publications came from Europe,[14,15,18,19,21,24,25,30] 5 from the US,[20,23,31-33] 5 from Asia[22,26,28,29,35] and one from Australia.[27] Almost half of the included studies were retrospective (9 of 19) and mainly conducted in the US and Asia[38,41,42,45,49,52,53] while half of the European studies were prospective (4 of 8).[14,15,18,24]

Patients' characteristics and treatment

In general, the studies lacked details on patients' baseline characteristics, and when the information was available, the patient populations were heterogeneous in terms of disease stage, disease duration, treatment and treatment duration. Patients were predominantly male and the mean age of patients across studies was 48 years. One study was conducted on children with CML.[29] Most of the studies included CML patients only; however, 3 studies also included patients with other diseases, which were gastrointestinal stromal tumors[19,23] and multiple myeloma.[27]

If a diagnosis code was used, it was based on ICD9 for CML patients. In 8 (42%) studies, patients were in CML-CP,[15,18,21,22,24,26,28,35] and in a further 2 studies patients could be in any of the 3 CML phases.[14,32] The disease duration varied across studies, ranging from less than three months to five years.

Only 7 studies reported risk scores or severity of CML, mainly with Sokal risk score distribution,[15,18,22,24] or with the Hasford score distribution,[18] or by CML severity (classified as usual, moderate or high,[20] and moderate or severe CML[31]). Only a few studies reported base-line comorbidities, primarily measured by the Charlson Comorbidity Index[23,31,32] and incidence of certain comorbidities such as cardiovascular disease or diabetes.[14,31,33]

Imatinib monotherapy was the most common treatment studied,[14,15,18,20-29,32,35] whereas only 2 studies measured adherence to dasatinib and nilotinib.[31,33] Mean treatment duration ranged between 6-63 months (Figure 2). Only

half of the studies reported initial doses of the drug used.[14,15,18,20,22,24,25,28,29,31,33,35]

Definition, measurement methods and adherence metrics

Adherence was not always clearly defined in the included studies and almost half of the studies (7 of 19) did not refer to any definition of adherence. Measurement methods for adherence varied according to the type of study (retrospective, prospective or cross-sectional) (Figure 3). Retrospective studies mainly used claims data and pharmacy refill data to measure adherence. The most commonly used metric to measure adherence in these retrospective studies was the medication possession ratio (MPR) defined as total days' supply of the drug from index date through to end of the follow-up period divided by the number of days in the follow-up period.[20,23,32,33] Various approaches were used in prospective studies, e.g. electronic compilation of drug dosing histories like Medication Event Monitoring Systems (MEMS®),[15,24] blood sampling to measure drug levels,[18] or diary logs and questionnaires in cross-sectional studies.[25,27] Few studies used a combination of measurement methods such as a questionnaire or patient diary log combined with pill count, appointments kept or MEMS®.[14,21] We assessed the adherence method sampling rate used in each study to provide information on the dynamics of adherence over time, as well as to prevent a clear distinction being made between suboptimal implementation of a dosing regimen and short persistence in case of low sampling rate. In general, the rates observed in this review were very low with yearly MPR computed over the entire period of follow up.[31,33] Automatic compilation of drug dosing history data using an electronic monitor resulted in a sampling rate of 4 per hour.[15]

Extent of non-adherence

The average adherence reported in studies varied from 19% to almost 100% of the proportion of prescribed drug

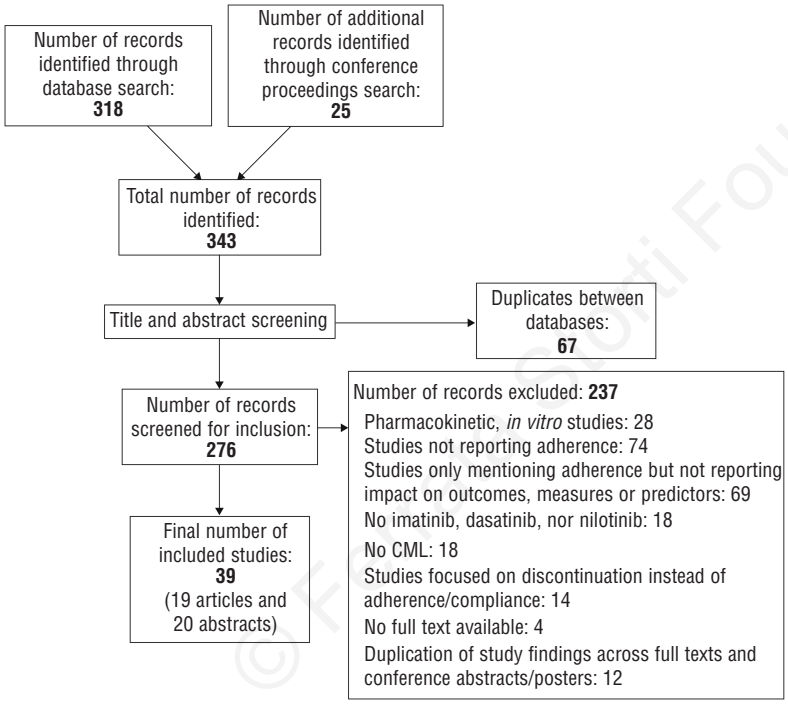

Figure 1. Flow diagram of included studies. The analysis was performed on 19 articles, whereas abstracts were only considered for inclusion in the Discussion.

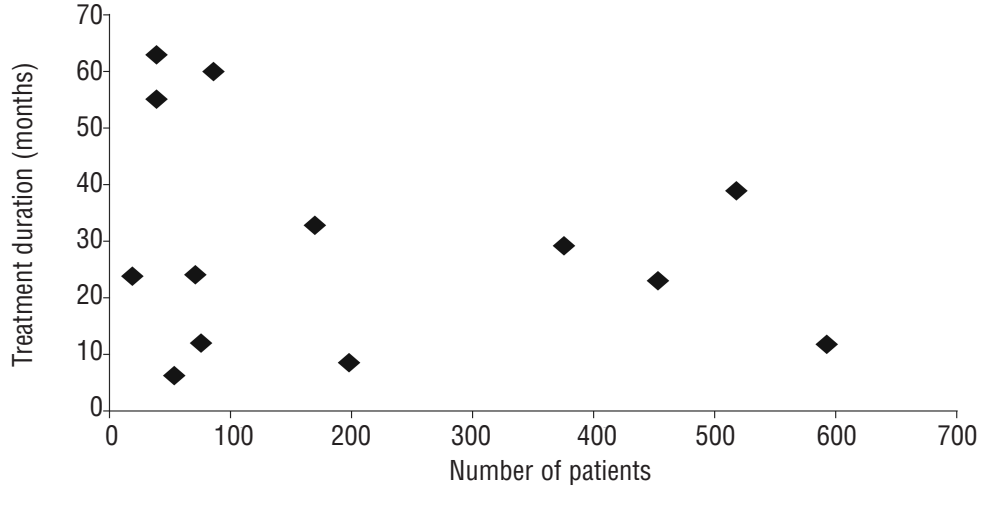

Figure 2. Patient treatment duration between studies.

taken during the total duration of the study, with differences according to the types of measurement methods used: 19-98% for MEMS®, 34-79% for MPR based on pharmacy refill data, 91% for pill count, 69-79% for proportion of days covered (PDC) based on claims data, between 67-97% for questionnaires, and between 70-98% for studies using other methods such as diary logs, appointments kept and dose prescribed versus dose obtained.[14,15,20,23,24,26,31,32] It was noted that higher estimates of adherence were found in the prospective studies compared with the retrospective studies.

When groups in the studies are displayed between adherent and non-adherent following a cut off (usually in the range of 80-90%, i.e. a patient was non-adherent if intake was less than 80-90% of total medication) and measured by MEMS®, MPR, or questionnaire, 3-56% of patients were classified as non-adherent (Figure 4).[14,15,22-25,32,34]

Non-adherence across BCR-ABL inhibitors

Clearly, there is a lack of available evidence showing a difference in adherence across BCR-ABL inhibitors. A retrospective cohort study reported a significantly higher adherence measured by an average PDC of 79% for patients treated with nilotinib compared with 69% for patients treated with dasatinib as second-line therapy (P=0.007).[31] In contrast, one study showed that when stratified by dose, patients receiving second-line nilotinib were almost 2 times more likely to have poor adherence using MPR less than 85% compared with patients receiv-

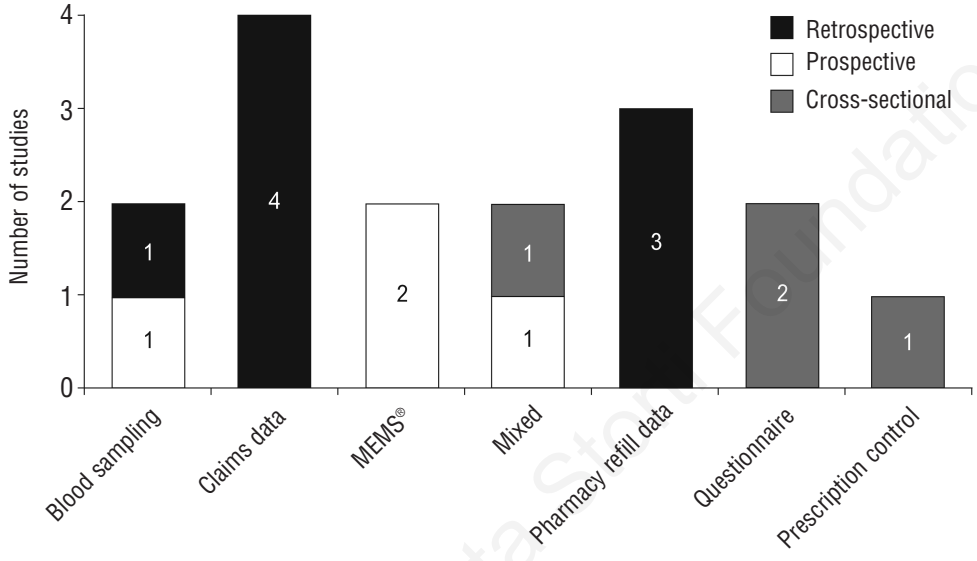

Figure 3. Methods used to measure adherence per type of study. Mixed refers to a combination of methods (e.g. a questionnaire in combination with MEMS® [Medication Event Monitoring Systems] or in combination with pill count and appointments kept).

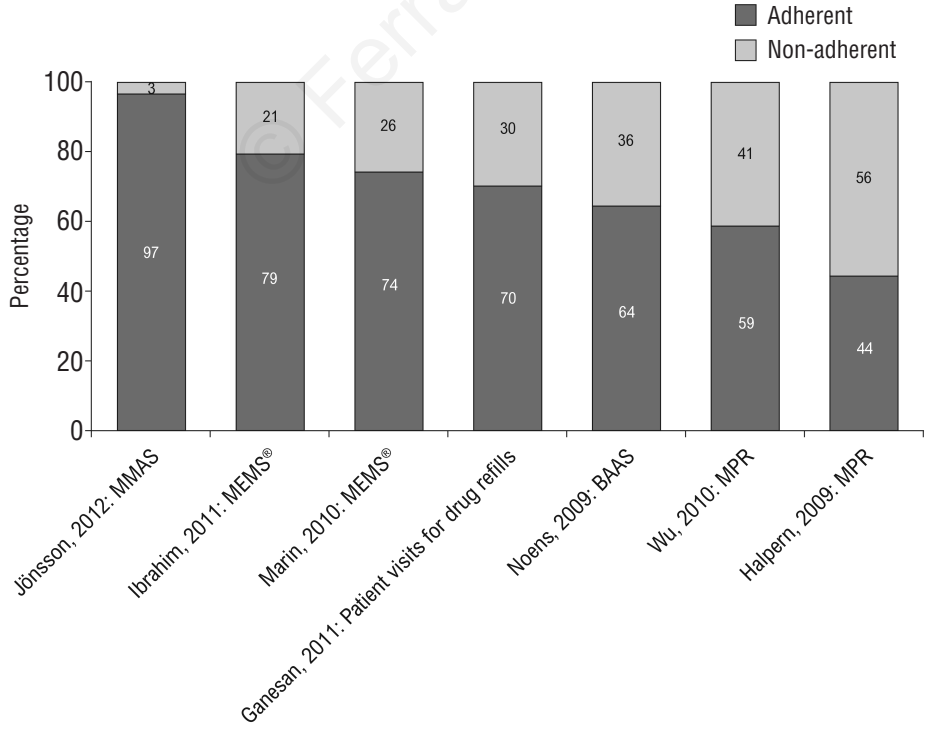

Figure 4. Adherent and non-adherent groups of patients in studies. MMAS: Morisky Medication Adherence Scale; MEMS®: Medication Event Monitoring Systems; MPR: medication possession ratio; BAAS: Basel Assessment of Adherence Scale with Immunosuppressive Medication.[14,15,22-25,32,34]

ing second-line dasatinib at the current approved dose of 100 mg once daily.[33]

The consequences of non-adherence

Six studies reported on the clinical impact of non-adherence and assessed only imatinib therapy.[14,15,22,24,25,35] In the prospective Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study, Noens and colleagues[14] showed that, on average, patients with suboptimal response had significantly higher mean percentages of imatinib not taken than did those with optimal response: 23% *versus* 7% using pill count (Figure 5A).[14] In addition, patients with a complete cytogenetic response (CCyR) had significantly lower mean percentages of imatinib not taken compared with those with an incomplete cytogenetic response (9% *versus* 23%). In a separate study of patients with CML who had achieved CCyR with imatinib,[15] 6-year major molecular response rates were significantly lower for non-adherent patients (14% for patients with adherence ≤90% using MEMS®) versus adherent patients (94% for adherence >90%) (P<0.001). Two recent studies confirmed the poor impact of suboptimal adherence on clinical outcomes (Figure 5B).[22,24]

No studies were identified in the literature review that investigated the impact of non-adherence on overall survival, safety, quality of life (QoL) or other patient reported outcomes.

However, 3 studies showed adherence impacted negatively on resource utilization and costs. All were USA retrospective claims database studies measuring adherence with MPR.[20,23,32] Higher adherence to imatinib was found to be associated with a substantial decrease in healthcare costs and resource use compared to lower imatinib adherence patient groups. Despite greater drug costs associated with patients with higher adherence, this is outweighed by a decrease in inpatient costs.

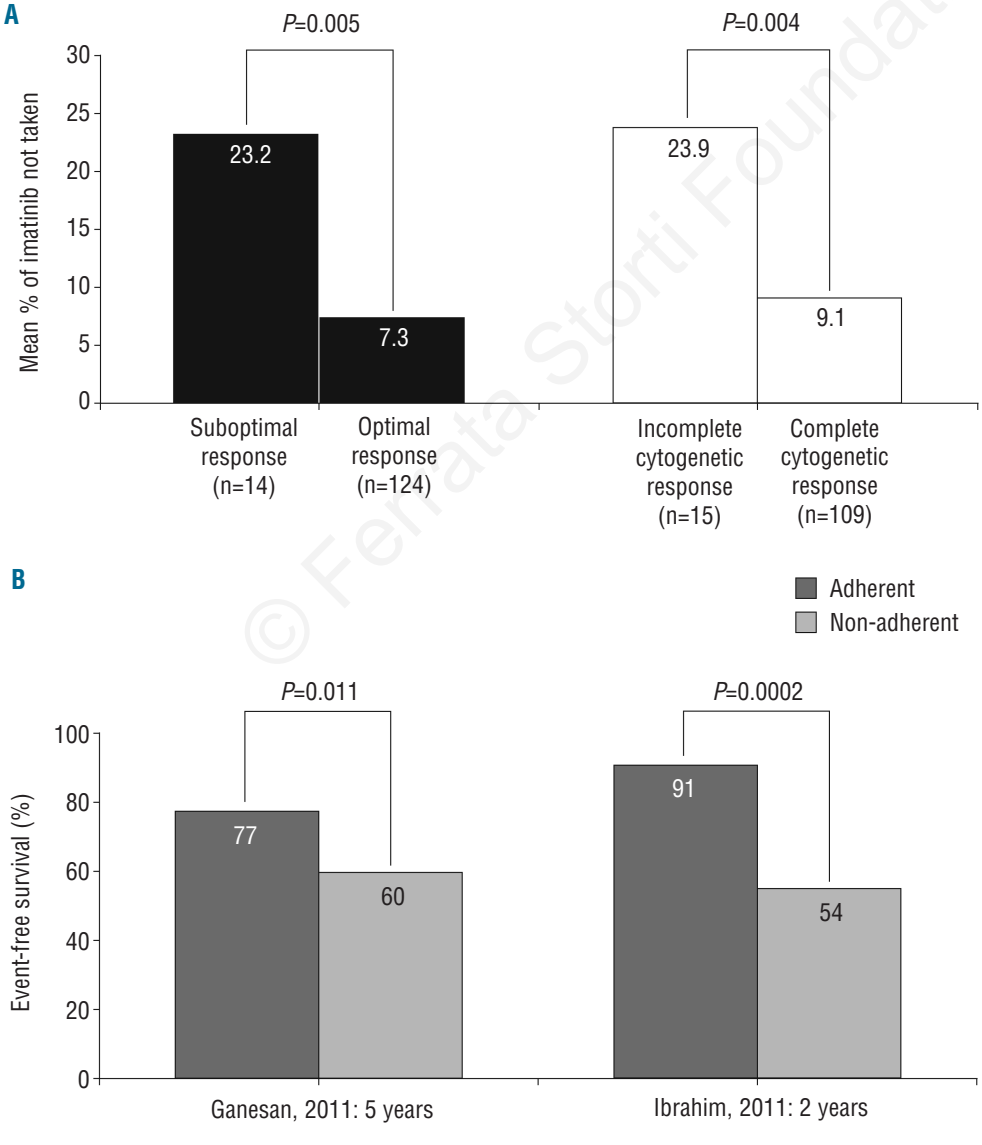

Figure 5. Impact on clinical outcomes. (A) Impact on cytogenetic response.[14] (B) Impact of poor adherence on event-free survival.[22,24]

Predictors of poor adherence

Eight studies investigated the impact that various factors had on influencing adherence. A general consensus was found for the predictive factors identified in the literature. From 'most frequent' to 'least frequent' these were: adverse events (AEs);[15,21] dose;[14,15,20,27] disease duration;[14] treatment duration;[14,23] a good patient-physician relationship and sufficient disease-related education.[14,25]

In CML, drug-related AEs were the most common reason for intentional non-adherence whereas forgetfulness was the most common reason for unintentional non-adherence.[21]

Contradictory findings were found across studies on relationship between adherence and age, gender, disease severity, comorbidities, dosing schedule and concomitant medication categories.

Interventions to improve adherence

The direct impact of interventions on adherence was only assessed in one study.[28] A patient counseling program, called the 'Happy club program' provides details such as the importance of optimal dosing, side effects, and drug-food interactions, and also provides patients with reminders, e.g. of the timing of their medication. This was found to be effective in helping patients to persist with imatinib medication, resulting in an improvement in overall adherence. Patient/physician interaction, patient education and aids for reminding patients to take their medications were considered important in improving medication adherence, but their direct impact on adherence was not tested.[14,21]

Quality analysis

The reasons for exclusion or withdrawal of patients were generally well reported and risk of attrition bias is, therefore, low. Since almost half the studies included were retrospective, these were most likely to be associated with a higher risk of bias than prospectively designed studies. Risks for selection and allocation concealment bias were observed in some prospective papers, e.g. use of a systematic sampling method for selection of the patients,[28] unclear allocation details,[18] or simply no information on patient selection.[26] Because blinding the method of adherence assessment is difficult and/or impossible in a study context, self-reporting through questionnaires is commonly used, generating bias (e.g. recall bias), and possibly overestimating adherence.

In general, the extent of medication adherence was explicitly reported in the studies. However, when investigated, the clinical outcome definitions were sometimes unclear, making its relationship with adherence difficult to interpret.[22,35]

Discussion

This study reveals that, despite the long-term survival benefit that is offered by recent BCR-ABL inhibitor therapy, many patients with CML are non-adherent to their medication. This is a critical concern for CML practitioners and patients since suboptimal adherence has been shown to negatively affect treatment success, in addition to increasing healthcare costs.

The dramatic impact of suboptimal adherence in patients with CML as shown in this review, explains the emphasis placed on understanding the problem through a deep analysis of the existing evidence. Unfortunately, we identified various methodological issues that hinder comparisons being made across studies, and especially across medications, in addition to multiple sources of potential bias. We noted great heterogeneity in the definitions of adherence, including a lack of explanation about the use of the 80-90% cut off to distinguish across adherent and non-adherent patients with CML. Methods of assessment were not systematically reported, despite literature indicating that results of adherence depend greatly on the method of assessment.[55] In addition, due to the varying study designs, different measurement methods of adherence were utilized, which could lead to different adherence estimates. As commonly found in the literature on adherence, higher estimates of adherence were observed in prospective studies, compared with retrospective studies.[56-59] A recent publication describing the taxonomy defining adherence to medications, defined this term as the process by which patients take their medication as prescribed, further divided into 3 quantifiable phases: 'initiation', 'implementation' and 'discontinuation'.[60] In the current review, none of the studies assessed adherence to BCR-ABL inhibitors across these different treatment phases.

Each assessment method is associated with strengths and limitations, but in practice none of these methods have been shown to be superior to the others. For example, adherence metrics based on pharmacy refill data assessment methods are more likely to identify treatment discontinuation, but are less sensitive to suboptimal implementation of the dosing regimen, which is a specific concern in CML. Therefore, other measures rather than refill records are required to assess treatment adherence in this disease. The use of refill records is based on the assumption that treatment gaps are due to patients not refilling prescriptions. However, patients can be incorrectly classified as non-adherent if the drug has been discontinued by the clinician, and dose interruptions can be dictated by a physician.[18,20,32] Biological markers may be more accurate for adherence measurement, but are costly, little used, and require additional tissue or blood samples and further laboratory testing. In support of the use of such markers, imatinib plasma levels may predict adherence and clinical response, and hence serve as a guide to optimizing therapy in CML patients.[47-49] More recently, studies have indicated that higher imatinib plasma levels correlate with clinical responses and compliance, and also suggest that plasma levels are a means to assess drug toxicity and management of imatinib therapy in patients with CML.[61,62]

Of interest, recently a self-assessment questionnaire received preliminary validation in patients with CML receiving imatinib treatment, allowing health care professionals to assess patient adherence during their routine clinical practice.[63]

A study using MEMS® over a 1-year period reported that adherence correlates to drug concentrations in plasma, thus indicating the successful use of electronically monitored dosing histories for modeling pharmacokinetic data.[64] Furthermore, a recent meta-analysis suggested that electronic-monitoring feedback is potentially an effective approach to enhance patient adherence to medications.[65] In the current review on adherence to BCR-ABL inhibitors for the treatment of CML, only 3 studies measured adherence through an electronic monitor. Nevertheless, the

potential impact of electronic monitors as an adherence intervention for providing feedback to CML patients and/or healthcare practitioners on adherence requires further validation in CML. Measuring adherence by comparing standard-of-care interventions with and without electronic reminders has not yet been performed in patients with CML.

Missing patient and/or treatment data prevented a full interpretation of certain studies on adherence, especially those attempting to compare adherence between medications.[20,22,23,26-29,31,32,35,52] It appears that adherence is superior in patients taking 2nd generation BCR-ABL inhibitors compared with imatinib, as presented in 2 conference abstracts from the literature.[36,43] Contradictory conclusions on adherence across 2nd generation drugs were observed in this review.[31,33]

From the study by Wu and colleagues,[31] we find it plausible that a large pool of patients treated by the previous label (higher) dosage of dasatinib (i.e. 140 mg/day) drove the favorable adherence to nilotinib over dasatinib. Even though the additional analyses by medication dosage subsequently published by Guerin and colleagues[66] confirmed this result, then the retrospective design of the study, in addition to the strong discrepancy on base-line comorbidities and CML severity across medication groups, still prevent us from drawing firm conclusions. A recently published retrospective analysis also reported better adherence with nilotinib over dasatinib while using a ratio between received daily dose and prescribed daily dose.[67]

In contrast, but confirming the results from Yood and colleagues,[33] 2 conference abstracts from the literature search reported a better adherence with dasatinib over nilotinib.[43,45] Among patients receiving second-line CML treatments, those receiving dasatinib (100 mg) had higher rates of adherence using MPR than those receiving nilotinib (800 mg) (75% *versus* 69%, respectively) from a US retrospective analysis.[45] This was also the case in a recent US and EU cross-sectional survey of CML patients using self-reported adherence to their BCR-ABL therapy through a designed questionnaire.[43] Patients receiving dasatinib reported fewer missed/skipped doses or had taken less than prescribed dose over the previous four weeks compared to patients receiving nilotinib. Even a marginally significant trend (P=0.062) was found between patients on dasatinib (23.7%) and patients on nilotinib (42.9%) for missing doses. However, it is important to mention that the observed difference on adherence should not be over-interpreted, as the difference could result from different methods being used across studies to measure adherence.

Comparative analyses on adherence between BCR-ABL inhibitors need to be further explored in more appropriately designed studies as most of this existing evidence is based on retrospective studies.[31,33,45,67]

Few studies adjusted their estimates by disease severity,[15,18,20,22,24,31,50] but most did not adjust by comorbidities, thereby potentially under-estimating the real impact of adherence.

The review improves our awareness on barriers to adherence, but this remains incomplete. Similar to many chronic diseases, increased medication dose and drug Aes are negatively associated with adherence in CML disease, and can predict for suboptimal adherence.[14,15,20,21] Patients with lower adherence rates may experience higher QoL if they experience fewer side effects, the conclusion being that adherence rates may be influenced more by how the patient copes with the AEs as opposed to whether or not they experience side effects.[21] However, no data are available to provide information on the relationship between adherence and QoL to support this hypothesis.

As also observed in other chronic diseases, such as HIV infection,[68,69] regimen complexity seems to be another barrier to CML medication adherence as described by the recent cross-sectional study in the US and EU.[43] Difficulties related to treatment following BCR-ABL inhibitor therapy has been shown to be a significant factor affecting adherence, with dietary and dosing restrictions being associated with greater difficulty. Non-adherence and self-reported difficulties related to treatment were significantly and positively correlated (r=0.22; P<0.003), implying that as treatment difficulty increases, non-adherence increases. Contradictory evidence is available in the literature regarding the impact of dosing frequency on adherence.[70-72] However, the addition of other constraints such as food or storage conditions may increase the risk for non-adherence. Furthermore, many patients treated with oral antineoplastics (including treatment for CML) do not understand the impact of timing their medications with food in relation to clinical outcomes,[73] hence compromising their ability to fully comply with the treatment regimen instructions.

Patient-reported personal factors associated with adherence behavior suggest that social support, being appropriately informed, and concomitant drug burden are the main factors impacting adherence to long-term imatinib therapy.[74]

Importantly, it is unknown whether there is any drug forgiveness for non-adherence (i.e. the non-adherence margin without clinically significant impact on outcomes, or in other words, the ability of a drug regimen to maintain the best clinically relevant therapeutic effect despite suboptimal adherence) and whether this can be defined for CML, or indeed ideally for all oral cancer therapies. Data from a follow-on analysis of the ADAGIO trial in imatinib-treated patients revealed that this margin of non-adherence is almost non-existent; the disease and/or the drug is 'unforgiving'.[75] Even minor deviations from the prescribed regimen appear to be associated with poorer clinical outcomes.[14] Because of this narrow margin of non-adherence, precise implementation of the imatinib dosing regimen is essential for the effective treatment of CML.[13]

Many of the included studies did not observe adherence over a long period of time. However, adherence to imatinib appears to decrease as treatment duration increases.[23] From a real-world retrospective study conference abstract,[34] we found that patients who received long-term imatinib therapy showed declining adherence as measured by MPR below 85%. In particular, evaluation of adherence by treatment dose and duration described that medication adherence was lower with a longer duration of treatment for all dose categories (i.e. the MPR and treatment interruptions were lower for patients whose treatment duration was greater than the median for all dose categories). Similarly, treatment interruptions increased as treatment duration increased. In another conference abstract,[40] long-term imatinib therapy showed a decrease in adherence of approximately 5% at the second year of follow up compared to the first year, which confirms a similar decrease observed at approximately 2.5 years of follow up in the Halpern *et al*. study.[23] This highlights the

importance of ensuring that available solutions to improve adherence are feasible for long-term therapy.

As observed also in other chronic diseases,[76] the literature on interventions to improve adherence with CML medications remains surprisingly weak considering the negative impact that suboptimal adherence has on health outcomes. Only a small subset of studies have suggested drivers of potentially effective interventions in CML, and only one tested a program to enhance adherence,[28] but there are no studies linking improved adherence to improvements in other outcomes such as morbidity, mortality, QoL, quality of care, patient satisfaction, healthcare utilization and costs.

This review found adherence problems with imatinib treatment to be associated with excessive resource use or costs which was also confirmed by a recent conference abstract showing a lower rate of resource use with a higher rate of adherence with dasatinib.[45] However, all studies analyzing the impact of adherence on costs were US based, limiting their generalizability. Furthermore, studies used charges as proxy for costs. However, charges have been criticized because they do not reflect real costs[77] and they do not take into account the various levels of co-payment, deductibles, and co-insurances. As observed in other chronic conditions,[78,79] hospitalization is a substantial cost driver of non-adherence. However, it is not clear if this result is driven by the inclusion of more severe or advanced patients with CML in the studies. Cost offsets due to improved adherence may not be as prominent for healthier patients.

This review yielded a broad search strategy that prevented the likelihood of missing relevant studies, as well as providing a large research scope so that the results of this literature review can support decisions on best study design for future research into adherence in CML. We included non-peer-reviewed research (conference abstracts) in the search; this is known to be associated with lower rigorous and scientific credibility than fully peer-reviewed publications. However, with regards to the paucity of peer-reviewed papers on adherence in CML, excluding this gray literature would have substantially eroded the extent of the information raised from our research. Findings from these conference abstracts were, however, reported in the present Discussion section if they were considered to be able to balance or confirm results obtained from peer-reviewed publications, as well as if they explored new interesting facets of the problem of adherence in CML (e.g. impact of treatment difficulty, comparative analyses on adherence across 2nd generation BCR-ABL inhibitors, or impact of treatment duration).

It is worth noting that adherence is more than just sticking with a regimen, since it also comprises persistence, i.e. how long the patient follows the treatment plan. However, in the present review, we excluded the search term 'persistence' to avoid retrieving the studies on cure of the disease,[80] although this might have resulted in excluding key studies.

Recommendations

As a result of this systematic review and the follow-up discussion with the advisory committee, recommendations can be made for future studies of adherence to BCR-ABL inhibitor treatment in CML.

A robust taxonomy should be adopted to describe and define adherence to CML medications, and any attempt to quantify and compare the extent of medication adherence should distinguish across the different treatment phases, 'initiation', 'implementation' and 'discontinuation'. There is a clear need for prospective studies with reliable and richly sampled measurement of adherence to better characterize implementation and define each drug's forgiveness margin in order to remove the caveats associated with retrospective studies. Depending on the study settings and objectives, different adherence measurement methods that are straightforward to implement in daily practice can be investigated and combined. For example, electronic prescription databases are best suited to estimate treatment initiation and pharmacy refill data support treatment discontinuation (i.e. persistence), whereas electronic monitoring is useful for treatment implementation. Hence, a combination of methods for assessing treatment adherence is desirable, ideally with electronic methods and monitoring being mandatory in the particular context of clinical studies. Easier methods should be implemented in daily practice, including but not limited to electronic methodology such as mobile phone reminders. The more sophisticated methodologies such as MEMS® are unlikely to find their application in routine practice. Finally, the observation of an optimal therapeutic effect remains one of the most reliable adherence assessment methods. Establishing non-adherence margins, assessing the degree of 'forgiveness' for BCR-ABL inhibitors against the observed deviation from the prescribed dosing regimen, and defining the adherence patterns that have the highest likelihood of compromising each treatment efficacy, are all crucial.

Additional research is needed across BCR-ABL inhibitors on adherence, especially between the 2nd generation BCR-ABL inhibitors dasatinib and nilotinib, with appropriate study designs and populations to guide decisions regarding prescription medicine. Furthermore, simplifying treatment regimens may result in improved adherence.

More and consistent information is needed on clarifying the predictors of suboptimal adherence as well as on identifying specific risk groups for suboptimal adherence early in the course of the disease.

Performing long-term follow-up research on the impact that suboptimal adherence has on outcomes will help identify intervention components supporting patients to stay on treatment. Furthermore, the interventions should be specific to each patient, taking into account both intentional and unintentional reasons for non-adherence to the prescribed treatment.[21]

As expressed during the advisory committee discussion, the findings of this literature review reveal that suboptimal adherence in CML is likely to be under-estimated and that the subsequent burden can be dramatic for the patients. The participants recognized a need for greater education on adherence of treatment stakeholders, as also mentioned in recent publications.[14,25,44,81,82] Nurses who are strong patient advocates should also participate in adherence monitoring during the therapy.[83] If patients are ultimately accountable for adhering to their prescribed treatment, they can be supported through effective communication and partnership with their healthcare providers.

Demonstrating the economic benefit of implementing adherence-improving programs in CML, along with the clinical benefits achieved with adherence, may be required to widely promote their adoption by the decision makers.

Conclusion

This review confirms that suboptimal adherence to CML medication has a deleterious impact on the course of the illness and is associated with increased healthcare costs. However, despite the importance of medication adherence in CML, its evaluation is still an open field of research, as gaps in the existing evidence and the heterogeneous methods used mean that the findings are difficult to interpret. In particular, further identification and recognition of non-adherence problems through the use of valid definitions and tools are warranted so that simple and effective preventive strategies can be researched and tested in treated CML populations. In accordance with this, any comparison between treatments and studies will not be reliable without the appropriate adherence metrics in place. The heterogeneity of the studies prevented an accurate identification of CML patients who might be at risk for suboptimal adherence, which reinforces the need for greater scrutiny by medicine providers of adherence, as well as a strong partnership and communication with the patients.

Acknowledgments

The authors would like to thank StemScientific, funded by Bristol-Myers Squibb, for providing editorial support.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Baccarani M, Dreyling M, ESMO Guidelines Working Group. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl. 5):v165-7.
2. NCCN.org [Internet]. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology (NCCN Guidelines™). Chronic myelogenous leukemia. Version 2.2011 [accessed 2011]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
3. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. 1999;340(17):1330-40.
4. Alvarez RH, Kantarjian H, Cortes JE. The biology of chronic myelogenous leukemia: implications for imatinib therapy. Semin Hematol. 2007;44(1 suppl. 1):S4-14.
5. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-51.
6. Pharma.US.Novartis.com [Internet]. Novartis Pharmaceuticals Corporation: GLEEVEC (imatinib mesylate) tablets for oral use prescribing information. East Hanover, NJ, USA, 2013 [accessed 2013]. Available from: www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf.
7. Packageinserts.BMS.com [Internet]. Bristol-Myers Squibb Company: Sprycel® (dasatinib) capsules prescribing information. Princeton, NJ, USA, 2006 [accessed 2011]. Available from: http://packageinserts.bms.com/pi/pi_sprycel.pdf.
8. Pharma.US.Novartis.com [Internet]. Novartis Pharmaceuticals Corporation: Tasigna® (nilotinib) capsules prescribing information. East Hanover, NJ, USA, 2012 [accessed 2013]. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/tasigna.pdf.
9. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70.
10. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-9.
11. Hochhaus A, Shah NP, Cortes JE, Baccarani M, Bradley-Garelik MB, Dejardin D, et al. Dasatinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): DASISION 3-year follow-up. J Clin Oncol. 2012;30(suppl.):Abstract 6504.
12. Kantarjian H, Flinn IW, Goldberg S, Bunworasate U, Zanichelli MA, Nakamae H, et al. Nilotinib versus imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 3-year (yr) follow-up (f/u). J Clin Oncol. 2012;30(suppl.)Abstract 6509.
13. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Ann Rev Pharmacol Toxicol. 2012;52:275-301.
14. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachée P, Berneman Z, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood. 2009;113(22):5401-11.
15. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Buaet M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol. 2010;28(14):2381-8.
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:332-6.
17. Cochrane-Handbook.org [Internet]. Cochrane Collaboration: Cochrane handbook for systematic reviews of interventions. 2011 [accessed 2011]. Available from: http://www.cochrane-handbook.org/.
18. Baccarani M, Martinelli G, Rosti G, Trabacchi E, Testoni N, Bassi S, et al. Imatinib and pegylated human recombinant interferon-alpha2b in early chronic-phase chronic myeloid leukemia. Blood. 2004;104(13):4245-51.
19. Breccia M, Efficace F, Alimena G. Imatinib treatment in chronic myelogenous leukemia: What have we learned so far? Cancer Lett. 2011;300(2):115-121.
20. Darkow T, Henk HJ, Thomas SK, Feng W, Baladi JF, Goldberg GA, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. Pharmacoeconomics. 2007;25(6):481-96.
21. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. Leuk Res. 2011;35(5):626-30.
22. Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S, et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. Am J Hematol. 2011;86(6):471-4.
23. Halpern R, Barghout V, Zarotsky V, Williams D. Costs and utilization associated with imatinib adherence in patients with chronic myeloid leukemia or gastrointestinal stromal tumors. J Clin Outcomes Manag. 2009;16(5):215-23.
24. Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood. 2011;117(14):3733-6.
25. Jönsson S, Olsson B, Söderberg J, Wadenvik H. Good adherence to imatinib therapy among patients with chronic myeloid leukemia-a single-center observational study. Ann Hematol. 2012;91(5):679-85.
26. Kiguchi T, Tauchi T, Ito Y, Miyazawa K, Kimura Y, Ohyashiki K. Compliance with taking imatinib mesylate in patients with chronic myeloid leukemia in the chronic phase. Leuk Res. 2009;33(3):506-8.
27. Kong DC, Dooley MJ, Stewart K, Larizza MA. Factors influencing adherence to molecular therapies in haematology-oncology outpatients. J Pharm Prac Res. 2006;36(2):115-8.
28. Moon JH, Sohn SK, Kim SN, Park SY, Yoon SS, Kim IH, et al. Patient counseling program to improve the compliance to imatinib in chronic myeloid leukemia patients. Med Oncol. 2012;29(2):1179-85.
29. Muramatsu H, Takahashi Y, Sakaguchi H, Shimada A, Nishio N, Hama A, et al. Excellent outcomes of children with CML treated with imatinib mesylate compared to that in pre-imatinib era. Int J Hematol. 2011;93(2):186-91.

30. Prejzner W. Compliance during therapy of patients with chronic myeloid leukemia. Hematologica. 2010;1(3):239-43.
31. Wu EQ, Guerin A, Yu AP, Bollu VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. Curr Med Res Opin. 2010;26(12):2861-9.
32. Wu EQ, Johnson S, Beaulieu N, Arana M, Bollu V, Guo A, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. Curr Med Res Opin. 2010;26(1):61-9.
33. Yood MU, Oliveria SA, Cziraky M, Hirji I, Hamdan M, Davis C. Adherence to treatment with second-line therapies, dasatinib and nilotinib, in patients with chronic myeloid leukemia. Curr Med Res Opin. 2012;28(2):213-9.
34. Yood MU, Oliveria SA, Hirji I, Cziraky M, Davis C. Adherence to treatment in patients with chronic myelogenous leukemia (CML) during a 10-year time period: a medical record review. Blood. 2010;116(21):Abstract 4492.
35. Yoshida C, Komeno T, Hori M, Kimura T, Fujii M, Okoshi Y, et al. Adherence to the standard dose of imatinib, rather than dose adjustment based on its plasma concentration, is critical to achieve a deep molecular response in patients with chronic myeloid leukemia. Int J Hematol. 2011;93(5):618-23.
36. Almeida M, Pagnano K, Souza H, Miranda E, De Souza C. High adherence to Tyrosine Kinase Inhibitors seems to be related to best cytogenetic response in the hasford lower risk group in Chronic Myeloid Leukemia. Blood. 2010;116(21):Abstract 4477.
37. Almeida MH, Pagnano KB, Miranda EC, Souza CA. Higher adherence related to complete molecular response (CMR) in chronic myeloid leukemia patients using imatinib mesilate. Haematologica. 2011;96(suppl. 2):Abstract 678.
38. Almeida MH, Barbosa Pagnano KB, Sanges 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. 2010;95(suppl. 2):Abstract 820.
39. Daouphars M, Ouvry M, Lenain P, Rouvet J, Varin R. Adherence assessment in Chronic Myeloid Leukaemia patients treated by tyrosine kinase inhibitors. Int J Clin Pharm. 2011;33:414-15.
40. Doti CA, Stemmelin GR, Moiraghi EB, Flores MG, Garcia J, Murro H, et al. Adherence to imatinib mesylate treatment: two years follow up. Blood. 2008;112(11):Abstract 4267.
41. Fogliatto L, Capra M, Schaan M, Fassina K, Fernandes MS, Schilling MA, et al. Impact of comorbidity in event-free survival, toxicity and adherence to treatment in chronic myeloid leukemia patients treated with imatinib. Blood. 2010;116(21):Abstract 2296.
42. Funke VAM, Moellmann-Coelho A, Asano E, Nita ME, Donato BM, Rahal E. Impact of non-adherence to Imatinib on progression-free survival a 1st treatment for Chronic Myeloid Leukemia in Brazil: two years follow up. Value Health. 2011;14(3):A168-9.
43. Gupta S, Goren A, Victor TW, Chapnick J, Hawthorne S, Hirji I, et al. Associations between treatment restrictions, patient-reported treatment burden and adherence to tyrosine-kinase inhibitor therapy among Chronic Myeloid Leukemia patients in the United States and Europe. Blood. 2011;118(21):Abstract 2077.
44. Guilhot F, Coombs J, Zernovak O, Szczudlo T, Rosti G. A global retrospective and physician-based analysis of adherence to tyrosine kinase inhibitor (TKI) therapies for chronic myeloid leukemia (CML). Blood. 2010;116(21):Abstract 1514.
45. Hirji I, Joo S, Davis C. Treatment adherence and resource use costs in chronic myeloid leukemia [poster]. American Society of Health-System Pharmacists Congress. 2011:Abstract 40-M.
46. Johnson CN, Cowan L, Gorospe GL, Ailawadhi S. Disease knowledge in chronic myeloid leukemia (CML) patients as a predictor of compliance to treatment. Blood. 2010;116(21):Abstract 4481.
47. Koren-Michowitz M, Volchek Y, Ben-Yehuda D, Naparstek E, Gavish I, Levi E, et al. Imatinib trough plasma levels in Philadelphia positive chronic myeloid leukemia (CML) patients: results of a multicenter study CSTI571AIL11TGLIVEC. Hematologica. 2010;95(suppl. 2):Abstract 0809.
48. Kutsev S, Oxenjuk O, Kravchenko E, Shatokhin Y, Bogdanova Y, Burnasheva E, et al. The role of imatinib plasma level test in evaluation of the nonadherence to therapy in chronic myelogenous leukemia patients. Hematologica. 2010;95(suppl. 2):Abstract 0817.
49. Lee S, Johnson C, Sandoval Y, Gorospe G, Yang AS, Ailawadhi S. Imatinib meslylate plasma levels predict compliance in patients with chronic myelogenous leukemia. Blood. 2009;114(22):Abstract 4274.
50. Palandri F, Castagnetti F, Iacobucci I, Amabile M, Gugliotta G, Poerio A, et al. The combination of interferon-alpha with imatinib in early chronic phase chronic myeloid leukemia patients induces a significant improvement of the molecular responses in the first two years of treatment: results from three studies from the GIMEMA CML Working Party. Blood. 2009;114(22):Abstract 2192.
51. Rosti G, Castagnetti F, Poerio A, Breccia M, Levato L, Capucci A, et al. High and early rates of cytogenetic and molecular response with nilotinib 800 mg daily as first line treatment of Ph-positive chronic myeloid leukemia in chronic phase: results of a phase 2 trial of the GIMEMA CML Working Party. Blood. 2008;112(11):Abstract 181.
52. St Charles M, Bollu VK, Hornyak E, Coombs J, Blanchette CM, DeAngelo DJ. Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia. Blood. 2009;114(22):Abstract 2209.
53. Wu EQ, Guerin A, Bollu VK, Guo A, Cloutier M, Ponce de Leon Barido D, et al. Impact of pleural effusion (PE) on treatment adherence, discontinuation, switching, and dose modification in patients with chronic myelogenous leukemia (CML). J Clin Oncol. 2011;29(suppl.):Abstract 6616.
54. Wu S, Chee D, Ugalde A, Butow P, Seymour J, Schofield P. What doctors don't know about adherence: a qualitative study of adherence to imatinib amongst patients with chronic myeloid leukaemia. Psychooncology. 2011;20(suppl. 2):Abstract P1-127.
55. Gossec L, Tubach F, Dougados M, Ravaud P. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review. Am J Med Sci. 2007;334(4):248-54.
56. Gordis L. Conceptual and methodological problems in measuring compliance. In: Haynes RB, Taylor DW, Sackett DL, eds. Compliance in Health Care. Baltimore, MD: Johns Hopkins University Press. 1979;23-5.
57. Haynes RB, Taylor DW, Sackett DL, eds. Compliance in Health Care. Baltimore, MD: Johns Hopkins University Press. 1979;49-62.
58. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is the patient taking the treatment as prescribed? JAMA. 1993;269(21):2779-81.
59. Eze UIH, Ojieabu WA, Femi-Oyewo MN, Martins OO. Evaluation of adherence in elderly diabetic hypertensive patients. J Hosp Clin Pharm. 2011;1(4).
60. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691-705.
61. Koren-Michowitz M, Volchek Y, Naparstek E, Gavish I, Levi I, Rowe JM, et al. Imatinib plasma trough levels in chronic myeloid leukaemia: results of a multicentre study CSTI571AIL11TGLIVEC. Hematol Oncol. 2012;30(4):200-5.
62. Rezende VM, Rivellis AJ, Gomes MM, Dörr FA, Novaes MM, Nardinelli L, et al.. Determination of serum levels of imatinib mesylate in patients with chronic myeloid leukemia: validation and application of a new analytical method to monitor treatment compliance. Rev Bras Hematol Hemoter. 2013;35(2):103-8.
63. Daouphars M, Ouvry M, Lenain P, Rouvet J, Jardin F, Bubenheim M, et al. Preliminary validation of self-assessment tool to measure imatinib adherence in patients with chronic myeloid leukemia. Pharmacotherapy. 2013;33(2):152-6.
64. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquhart J. Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models. J Clin Pharmacol. 2005;45(4):461-7.
65. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs. 2013;73(6):545-62.
66. Guérin A, Chen L, Wu EQ, de Leon DP, Griffin JD. A retrospective analysis of therapy adherence in imatinib resistant or intolerant patients with chronic myeloid leukemia receiving nilotinib or dasatinib in a real-world setting. Curr Med Res Opin. 2012;28(7):1155-62.
67. Santoleri F, Sorice P, Lasala R, Rizzo RC, Costantini A. Patient adherence and persistence with Imatinib, Nilotinib, Dasatinib in clinical practice. PLoS One. 2013;8(2):e56813.
68. Stone VE, Hogan JW, Schuman P, Rompalo AM, Howard AA, Korkontzelou C, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. J Acquir Immune Defic Syndr. 2001;28(2):124-31.
69. Sax PE, Meyers JL, Mugavero M, Davis KL.

Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. PLoS One. 2012;7(2): e31591.
70. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA. 1989;261 (22):3273-7.
71. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther. 2002;24(2):302-16.
72. Comté L, Vrijens B, Tousset E, Gérard P, Urquhart J. Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics. J Pharmacokinet Pharmacodyn. 2007;34(4):549-58.
73. Muluneh B, Alexander M, Deal AM, Deal M, Markey J, Neal J, et al. Prospective evaluation of perceived barriers to medication adherence by patients on oral antineoplastics. J Clin Oncol. 2012;30(suppl.):Abstract 6042.
74. Efficace F, Baccarani M, Rosti G, Cottone F, Castagnetti F, Breccia M, et al. Investigating factors associated with adherence behaviour in patients with chronic myeloid leukemia: an observational patient-centered outcome study. Br J Cancer. 2012; 107(6):904-9.
75. Abraham I, Lee C, MacDonald K, van Lierde M-A, Beaver M, Geest SD, et al. No margin for nonadherence: novel application of Kaplan-Meier methods to model the efficacy of adherence to imatinib treatment by patients with chronic myeloid leukemia (the ADAGIO Study). European Society for Patient Adherence, COMpliance, and Persistence Ghent, Belgium, October 25-27, 2012:Abstract 4.
76. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock S, Wines RCM, et al. Closing the quality gap: revisiting the state of the science (Vol. 4: Medication adherence interventions: comparative effectiveness). Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Sep. (Evidence Reports/Technology Assessments, No. 208.4.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK114350/
77. Finkler SA. The distinction between cost and charges. Ann Intern Med. 1982; 96(1):102-9.
78. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43(6):521-30.
79. Halpern R, Becker L, Iqbal SU, Kazis LE, Macarios D, Badamgarav E. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. J Manag Care Pharm. 2011;17(1):25-39.
80. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010;11(11):1029-35.
81. Gater A, Heron L, Abetz-Webb L, Coombs J, Simmons J, Guilhot F, et al. Adherence to oral kinase inhibitor therapies in chronic myeloid leukemia. Leuk Res. 2012;36(7): 817-25.
82. Wu S, Chee D, Ugalde A, Butow P, Seymour J, Schofield P. Patient's and health professionals' perspectives of adherence and imatinib therapy in treatment of chronic myeloid leukaemia. Asia Pac J Clin Oncol. 2011;7(suppl. 4):Abstract 305.
83. Winkeljohn DL. Oral chemotherapy medications: the need for a nurse's touch. Clin J Oncol Nurs. 2007;11(6):793-6.