Review

Treatment adherence in chronic myeloid leukemia: a systematic review of the literature

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Practice Points

- Nonadherence to tyrosine kinase inhibitors is associated with reduced clinical response and increased healthcare costs.
- About a quarter to a third of chronic myeloid leukemia patients prescribed tyrosine kinase inhibitors are generally found to be nonadherent, although wide variations in adherence rates are evident and partly depend on the measurements and the definitions of nonadherence used.
- Nonadherence can be intentional – when the patient decides to miss the doses, or unintentional – when the patient for some reason cannot take the doses as prescribed. The most common reason for intentional nonadherence is to deal with side effects and the most common reason for unintentional nonadherence is forgetting. It is important to differentiate between intentional and unintentional causes as they will require different interventions.
- It has not been possible to find reliable predictors of nonadherence to tyrosine kinase inhibitor therapy. It is therefore important to develop health systems where all patients are supported and to strive towards open and honest communication between patients and healthcare providers regarding adherence issues. Hospitals should develop specific protocols defining how to best support patients' treatment adherence.

SUMMARY The introduction of the tyrosine kinase inhibitor (TKI) imatinib in the late 1990s, and the more recently licensed TKIs dasatinib and nilotinib, have essentially transformed chronic myeloid leukemia from a terminal illness with poor prognosis to a chronic illness that can be managed by the patient at home. The success of the treatment, however, is now reliant on the patients' ability and motivation to adhere to the treatment as prescribed. Unfortunately many patients miss doses of their TKI treatment, which has been shown to have adverse consequences for individual patients' treatment response as well as increase the associated healthcare costs. Nevertheless, it has been difficult to identify reliable predictors and explanations for why patients

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miss doses, making it a complex challenge to develop interventions to reduce nonadherence and improve outcomes in this patient group. This systematic review identified 17 different studies that have investigated adherence to TKI treatment in chronic myeloid leukemia patients and gives an overview of the knowledge that has been accumulated in this field up until June 2011.

To follow prescribed treatment regimens can be demanding for individuals, in particular if it infringes on every day routines and activities. Many people living with a chronic illness therefore do not follow treatment recommendations as prescribed. The related literature is vast but compared with other illness groups cancer has received limited attention in relation to the way cancer patients' use their medication, in particular concerning malignancies other than breast cancers. It has been widely assumed that cancer patients are likely to take their medication as prescribed because of the seriousness of their illness. However, reviews on cancer patients' medication-taking behaviors, as well as on treatment adherence of patients with other serious illnesses, such as HIV/AIDS, have shown that this is not the case [1–3].

The extent to which a patient's behavior matches the prescriber's recommendations is generally referred to as the patients' adherence or compliance with treatment; of which adherence has become the preferred term because it is considered to be less paternalistic [101,102]. In recent years the importance of differentiating between intentional and unintentional nonadherence has also been recognized as their different causes may require different solutions [101,102]. Intentional nonadherence refers to patients making a conscious decision to alter or discontinue treatment; for example to reduce adverse events, whilst unintentional nonadherence occurs when the patient intends to adhere to their treatment but is hindered to do so by factors beyond their immediate control; for example, by forgetting to take a dose or not being able to swallow a tablet.

Nonadherence also presents an economical strain on healthcare systems, because of increased likelihood of hospitalizations, complications and morbidity [4–6]. Through auditing the amount of medications returned to pharmacies and conducting a public survey of the amount of unused medication kept by individuals at home it has been estimated that the cost of unused and unwanted medication exceeds £300 million in the UK [103]. In the USA the cost of nonadherence has been estimated to be US$100 billion, an estimation that is taking into account variables, such as increased use of health resources and loss of productivity [7]. Because of the substantial cost of nonadherence, both in terms of reduced clinical benefit for patients and in terms of increased costs to the healthcare system, nonadherence has become a priority for healthcare researchers and policy makers worldwide [102]. Indeed it has been suggested that improving nonadherence will have a greater impact on improving the population's health than the development of new medications [8]. Finally, nonadherence is often assumed to mean that a patient misses doses of medication; however, overingestion of medication can also have severe consequences, in particular when using highly toxic medication with narrow therapeutic indexes, such as oral anticancer agents [104].

The lack of awareness of nonadherence to anticancer treatments may be related to the fact that cancer care has previously mainly been delivered in a hospital setting through intravenous chemotherapy, radiotherapy and surgery. In these settings patients are closely monitored, thus minimizing the risk of nonadherence. However, the increased use of oral anticancer drugs, which is often preferred by the patients [9,10], has led to a reduction in monitoring by the clinical team. As a consequence, nonadherence is likely to become more of an issue than it is at present.

Nonadherence in chronic myeloid leukemia

Chronic myeloid leukemia (CML) accounts for approximately 15% of all leukemias in adults, which in turn constitute approximately 2% of the yearly cancer incidence in the UK [105]. In the UK it is estimated that 560 people are diagnosed with CML each year. CML is slightly more common in men than women and the median age at diagnosis is 60 years [106]. CML is unique amongst cancers in that a specific chromosomal abnormality, the *BCR-ABL1* fusion gene, has been identified as the cause of the illness, which has allowed for the development of highly effective drugs that target this abnormality [11].

Imatinib (Glivec/Gleevec®, Novartis, Basel, Switzerland) thus revolutionized the treatment of CML and after successful clinical trials was licensed in the USA as a first-line treatment in 2001, with the UK following suit in 2003. Imatinib selectively inhibits the enhanced tyrosine kinase activity of the protein encoded by the *BCR-ABL1* fusion gene and induces durable cytogenetic responses in the majority of patients with relatively few side effects [12]. It has been recently reported that CML patients in complete cytogenetic remission 2 years after starting imatinib can have a normal life expectancy [13]. Since the success of imatinib, several second-line tyrosine kinase inhibitors (TKIs) have been introduced including dasatinib (Sprycel®, Bristol-Myers Squibb, NJ, USA) and nilotinib (Tasigna® Novartis, Basel, Switzerland), which are the second-line TKIs that have so far been licensed, and a number of other TKIs that are currently being evaluated. However, if left untreated, CML is inexorably fatal and the continuous management of CML now depends on the patients' ability and motivation to adhere to their TKI treatment as prescribed. The aim of this paper was therefore to systematically review the literature related to nonadherence to TKIs in CML patients.

Search strategy

The systematic review was conducted in July 2011 (databases included Medline, Embase, PsychInfo, CINAHL, Cochrane Library and Web of Science). The search terms included adherence and the most commonly used synonyms of adherence, the different terms used to refer to CML and the relevant abbreviations, as well as the names of the TKIs currently used to treat CML (Table 1). The terms were tailored specifically according to each database and the detailed search strategies can be requested from the author. The search was restricted to humans, English publications and the time period January 1999 (when the first clinical trial of imatinib in CML patients was initiated) to June 2011.

All articles and conference abstracts of studies with the primary aim of investigating CML patients' adherence to TKIs were included whilst clinical trials that may or may not have also measured adherence rates were excluded. In order to get an overview of the whole research field the decision was taken to include all relevant conference abstracts, although these will not have gone through the same rigorous peer review process as journal publications. Some caution should therefore be taken when interpreting these results. Similarly, the majority of studies conducted in this field have been funded or sponsored by industry and these publications have also been included. To make this review transparent the type of publication that has been referenced (i.e., journal article, conference abstract), as well as information on potential conflict of interests have been highlighted in Table 2, which summarizes the studies reviewed.

After duplicates had been removed 754 abstracts were reviewed, of which 51 full text articles/conference abstracts were retrieved (Figure 1). Finally, 31 articles and conference abstracts reporting on 17 different studies were included in this review (Table 2).

The extent of nonadherence in CML patients

About one third of patients are generally considered to be nonadherent to their TKIs; nonetheless nonadherence rates in the studies reviewed showed a wide variation ranging 0.6–57% (Table 2) [14,15]. This wide variation partly

Table 1. Search terms used for the systematic literature review.

Search term		Search term		Search term		Search term
CML	AND	Patient	AND	Adherence	AND	Imatinib
CGL		Treatment		Compliance		Gleevec
Chronic myeloid leukaemia				Persistence		Glivec
Chronic myeloid leukemia				Concordance		TKI
Chronic myelogenous leukemia				Non-adherence		Tyrosine kinase inhibitor
Chronic granulocytic leukemia				Nonadherence		Nilotinib
				Non-compliance		Tasigna
				Noncompliance		Dasatinib
						Sprycel
						Bosutinib
						Ponatinib

Table 2. Summary of studies that have investigated the extent and impact of nonadherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia patients.

Study	Drug	Patients (n)	Adherence rate (measure used)	Results
Darkow *et al.* [16]	Imatinib	267	77.7% (mean MPR based on claims databases) and 31% of patients had treatment interruptions	Lower MPR was associated with higher healthcare costs. MPR was lower among women, in patients with higher numbers of cotherapies, patients with higher cancer complexity and in patients who initiated treatment on a higher imatinib dose Country: USA; sponsored or funded by industry
ADAGIO study Main publication: Noens *et al.* [20] Abstracts: [44–47]	Imatinib	169	33.3% of patients considered nonadherent and 14.2% of patients took all of their imatinib doses (VAS/BAAS/pill counts)	Patients with suboptimal clinical response had higher rates of nonadherence (pill count) than patients with optimal response. Patients with higher rates of nonadherence were older, had a longer period since having been diagnosed with CML, had been taking imatinib for a longer time, were prescribed imatinib ≥600 mg/day, received higher degree of chronic care, reported higher functional status and quality of life, were more likely to live alone and to be male. Patients who had better knowledge of their disease, who had a higher number of cotherapies and who had secondary or higher education had higher levels of adherence In terms of physician-related variables and impact on adherence, the duration of treatment follow-up visits and years of professional experience of the physician were related to higher nonadherence, while number of active patients seen in the past year and the duration of first visit with a patient diagnosed with CML was related to better adherence Country: Belgium; sponsored or funded by industry
Hammersmith study Main publications: Marin *et al.* [23] Ibrahim *et al.* [24] Eliasson *et al.* [34] Abstracts: [48–51]	Imatinib	87	26.4% of patients had an adherence rate of ≤90% and of these 14% had ≤80% (MEMS monitoring for 3 months)	All the patients included had achieved CCyR on imatinib at the time of enrollment. Patients with an adherence rate of ≤90% were less likely to achieve MMR and CMR. None of the patients who had ≤80% adherence achieved molecular responses. Patients who had lower adherence were more likely to be of younger age, have had their imatinib dose increased above 400 mg/day, were more likely to experience asthenia, nausea, muscle cramps and bone and joint pains and to take imatinib independent of food. Unexplained increases of BCR-ABL transcript levels during follow-up were also predictive of nonadherence [33]. At 2 years' follow-up, patients who had been nonadherent during the 3-month MEMS monitoring period were more likely to have lost their CCyR and to discontinue imatinib due to therapy failure [34] Country: UK; sponsored or funded by a public research grant (NIHR Biomedical Research Centre Funding Scheme) and authors have declared potential conflict of interests

BAAS: Basel Assessment of Adherence Scale; CCI: Charlson Comorbidities Index; CCyR: Complete cytogenetic response; CML: Chronic myeloid leukemia; CMR: Complete molecular response; EFS: Event-free survival; MEMS: Medication Event Monitoring System; MMR: Major molecular response; MPR: Medication possession ratio; PDC: Proportion of days covered; TKI: Tyrosine kinase inhibitor; VAS: Visual Analog Scale.

Table 2. Summary of studies that have investigated the extent and impact of nonadherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia patients (cont.).

Study	Drug	Patients (n)	Adherence rate (measure used)	Results
Main publication: Wu *et al.* [17] Abstracts: [52,53]	Imatinib	592	40.9% of patients had an adherence rate of less than 85% (MPR based on claims databases)	Patients with an adherence rate of <85% had more inpatient visits and longer inpatient hospital stays and incurred higher healthcare costs. There was no difference between patients with an adherence rate of <85% and patients with ≥85% in terms of age, gender, CML severity, health plan type, comorbidities and cotherapies. However, starting dose was found to be higher in patients with MPR <85%. The two abstracts report similar findings from analysis of the same data with the addition of data from a second claims database Country: USA; sponsored or funded by industry
Main publication: Wu *et al.* [30] Abstracts: [36]	Dasatinib Nilotinib (second line)	521 (452 dasatinib and 69 nilotinib)	Mean adherence rate for dasatinib was 69% and for nilotinib 79% (calculated as PDC [i.e., 0.69/0.79] based on claims databases)	Patients on nilotinib were found to have a higher adherence rate and to incur fewer and shorter inpatient hospital stays, and to incur lower healthcare costs Country: USA; sponsored or funded by industry
Ulcickas Yood *et al.* conference abstract [15]	Imatinib	216	51% of patients had an adherence rate of <85% (MPR based on medical records) and 57% of patients had treatment interruptions ≥1 (failure to refill prescription within 30 days)	The study aimed to establish adherence rates only Country: USA; sponsored or funded by industry
Ulcickas Yood *et al.* conference abstract [37]	Dasatinib Nilotinib (second line)	250 (197 dasatinib and 53 nilotinib)	Adherence rates not reported, but mentioned rates were calculated using MPR	Patients on dasatinib were found to have higher adherence rates than patients on nilotinib Country: USA; sponsored or funded by industry
Daouphars *et al.* conference abstract [27]	Dasatinib Imatinib Nilotinib	64 (46 imatinib, 13 dasatinib and five nilotinib)	12.5% of patients identified as nonadherent (self report) and 27.5% of patients had MPR <90% (pharmacy records)	Self report was predictive of MPR scores. There were no significant correlations between adherence levels and sex, age, treatment history or clinical response in this sample Country: France; authors affiliated with hospital or university and no conflict of interests declared
Fogliatto *et al.* conference abstract [28]	Imatinib	185	Adherence rates not reported, but mentioned patients were considered nonadherent if treatment interruptions for ≥20 consecutive days were identified (database records)	Comorbidities, measured using the ACE-27 and CCI, were predictive of EFS, risk of major toxicity and treatment adherence. CCI was found to be superior in predicting nonadherence Country: Brazil; authors affiliated with hospital or university and no conflict of interests declared

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Study	Drug	Patients (n)	Adherence rate (measure used)	Results
Tesch *et al.* conference abstract [14]	Imatinib	422	99.4% mean adherence rate (measurement method not reported)	It was concluded that, overall, patients had high adherence rates that translated to clinical responses in line with results from the Phase III clinical trial IRIS Country: Germany; authors affiliated with hospital or university and no conflict of interests declared
Lee *et al.* conference abstract [25]	Imatinib	19	42% of patients considered nonadherent (assessed by chart review and medical notes)	Patients were divided into groups depending on whether they had low (nine patients) or high (ten patients) plasma imatinib levels. Six out of nine patients were found to be nonadherent in the low group and two out of ten in the high group. There was no correlation between imatinib plasma levels and response, although there was a correlation between adherence and response. Patients were more likely to be nonadherent if their imatinib plasma levels were low Country: USA; authors affiliated with hospital or university and have declared potential conflict of interests
De Almeida *et al.* conference abstract [18]	Dasatinib Imatinib Nilotinib	131	94% (mean MPR based on claims databases) and 19.84% of patients had 100% MPR	Patients with decreased MPR were more likely to have been diagnosed with CML earlier and had longer duration of TKI treatment. Patients enrolled in clinical trials had higher adherence. Sex, age, socioeconomic status, marital status, level of education and TKI dose were not found to influence adherence Country: Brazil; authors affiliated with hospital or university and no conflict of interests declared
Guilhot *et al.* conference abstract [19]	TKI (unspecified)	1155 patients and 405 physicians	8% (Brazil) – 23% (Russia) of patients had an adherence rate of ≤90% and 43–53% were fully adherent (patient records review)	Higher adherence rates were related to achieving therapeutic milestones. Within Europe, adherence was higher in patients who received adherence counseling by a nurse or hematologist and in patients attending clinics where the institution had established adherence protocols. Comorbidities, age and number of cotherapies were not found to influence adherence Countries: Brazil, France, Italy, Spain and Russia (online survey); all authors have declared potential conflict of interests and three out of five authors declared employment by industry
Ganesan *et al.* [26]	Imatinib	516	29.6% had treatment interruptions of ≥1 week (patient records review)	Nonadherence adversely affected 5-year EFS and nonadherent patients were also less likely to achieve CCyR at any point during treatment. Age, sex, economic status and Sokal stage were not found to influence adherence Country: India; authors affiliated with hospital or university and no conflict of interests declared
Halpern *et al.* conference abstract [21]	Imatinib	374	55.6% of patients had an adherence rate of <90% in year 1 and 61.8% patients had adherence <90% in year 2 (MPR based on health claims databases)	Nonadherent patients had more and longer inpatients hospital stays, higher mean healthcare costs and higher care resource utilization Country: USA; sponsored or funded by industry

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Table 2. Summary of studies that have investigated the extent and impact of nonadherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia patients (cont.).

Study	Drug	Patients (n)	Adherence rate (measure used)	Results
Kiguchi *et al.* letter to editor [22]	Imatinib	52	93% in patients ≤40 years, 98% in patients 41–60 years, 96% in patients ≥61 years (MPR from pharmacy refill records)	Age, gender and duration of treatment were not found to influence adherence Country: Japan; authors affiliated with hospital or university and no conflict of interests declared
St Charles *et al.* conference abstract [29]	Imatinib	430	80% mean MPR and 40% of patients had adherence rate ≤85% (claims databases)	Duration of imatinib treatment, time lag between CML diagnosis and imatinib therapy initiation date, imatinib starting dose and patient cost sharing were found to be predictors of nonadherence Country: USA; all authors have declared potential conflict of interests and three out of six authors declared employment by industry

BAAS: Basel Assessment of Adherence Scale; CCI: Charlson Comorbidities Index; CCyR: Complete cytogenetic response; CML: Chronic myeloid leukemia; CMR: Complete molecular response; EFS: Event-free survival; MEMS: Medication Event Monitoring System; MMR: Major molecular response; MPR: Medication possession ratio; PDC: Proportion of days covered; TKI: Tyrosine kinase inhibitor; VAS: Visual Analog Scale.

reflects the different measurement methods and the definitions of nonadherence used; adherence definitions and measurements are specified in **Table 2** for the included studies. It is therefore impossible to calculate a composite rate of average adherence rates for the different TKIs or for different groups of patients. Higher rates of nonadherence have been identified using the medication possession ratio (MPR) based on USA claims databases [15–17] than, for example, in Brazil [18], which in addition to highlighting different adherence rates across patient populations from different countries, may reflect the influence of different healthcare systems and policies on adherence rates. Pharmacy refill records from Japan indicated low rates of nonadherence ranging 2–7% in the three age groups surveyed, with patients less than 40 years having lowest rates and patients between 41 and 60 years having the highest rates. A survey that reviewed patient records in Brazil, France, Italy, Spain and Russia reinforced the idea that patients' adherence rates may be different across countries [19].

There are few patients that are reported to be 100% adherent, reports range from 14.2% [20] and 53% [19], indicating that most patients at times miss at least some of their doses. Rates of nonadherence may also increase with time. Halpern *et al.* reported that rates of nonadherence were higher in the second year of follow-up (61.8%; MPR: <90%) compared with the first year (55.6%; MPR: <90%) [21] and other studies have reported that patients tend to have higher rates of nonadherence the longer time has passed since TKI therapy was initiated [18,19]; although there are also reports that duration of therapy do not influence adherence rates [22].

Clinical & economic consequences of nonadherence in CML patients

■ Clinical response

Clinical response to TKI therapy is closely related to patients' level of adherence [19,20,23–26]; although one study reported no relation between adherence and response to treatment [27,28]. This may seem obvious but this fact has only recently started to be accepted by the professional community as other factors, such as Sokal score, hOCT-1, which may also influence treatment response, have been considered to be more important predictors.

The ADAGIO study assessed adherence to imatinib prospectively over 90 days using

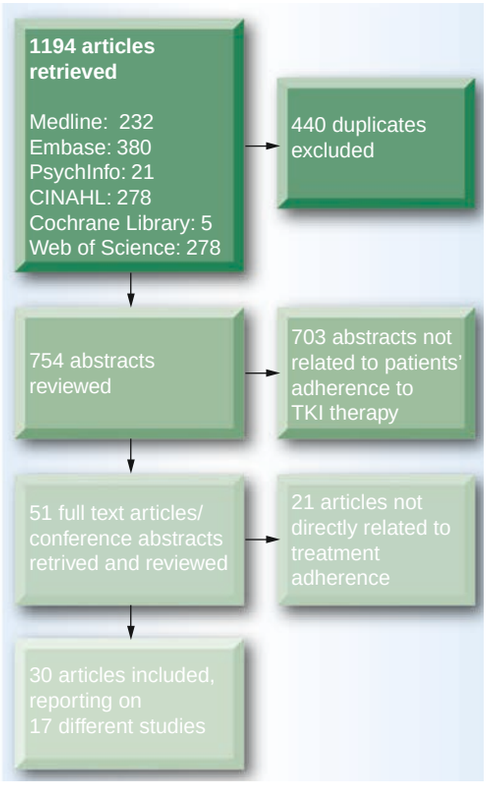

Figure 1. The number of articles identified from the different databases during the systematic review, the numbers excluded during the process and the number of articles included and reported in this paper.
TKI: Tyrosine kinase inhibitor.

self-report, third person reports and pill counts. They recruited 202 patients from 34 hematology centers in Belgium of whom 169 were included in the analysis. One third of the patients were identified as nonadherent and only 14.2% were perfectly adherent, defined as having taken 100% of the prescribed imatinib doses. Nonadherence according to pill count was found to be associated with reduced clinical response in this patient group. Patients with suboptimal response had higher mean percentages of imatinib not taken (23.2%; SD: 23.8) than did the patients with optimal response (7.3%; SD: 19.3; p = 0.005) [29].

A study at the Hammersmith Hospital in the UK recruited 87 patients with chronic phase-CML who had been prescribed imatinib for 2 years or more and had achieved at least complete cytogenetic response (CCyR). Adherence was monitored for 3 months using Medication Event Monitoring Systems (MEMS; Aardex®, Zug, Switzerland). MEMS is an electronic device fitted in the cap of a medication bottle of standard appearance that records the time and date on each occasion the bottle is opened. The adherence rate was calculated by dividing number of MEMS openings with the number of doses prescribed, thus assuming that opening the MEMS indicates an ingested dose. In this study, the 90% cut-off to dichotomize-adherent and -nonadherent patients was found to be the strongest predictor of clinical response. Patients were not told that the MEMS recorded openings, although they were told their adherence would be monitored using pill count. This approach was reviewed and approved by an NHS ethics committee. Median adherence rate was 98%; although 23 patients (26%) had adherence less than or equal to 90%, and of these, 12 patients (14%) took 80% or less. The trial results revealed that poor adherence was the predominant reason for failure to obtain adequate clinical responses [29]. The 2-year follow-up of this study reported that the 23 nonadherent patients were more likely to lose their CCyR (26.8 vs 1.5%; p = 0.0002) and were less likely to remain on imatinib therapy (64.5 vs 90.6%; p = 0.0006) than the 64 adherent patients [24].

Ganesan *et al.* included 516 Indian chronic phase-CML patients who received imatinib free of charge through a company-sponsored scheme [26]. Patients had to attend 3-monthly clinics where the drugs were dispensed and as nonadherence was defined as unwarranted treatment interruptions of more than 1 week. One third of patients were identified as nonadherent during the follow-up period (median 39 months). Nonadherent patients were less likely to achieve CCyR at any point during treatment (26 vs 44%, p = 0.004) and the 5-year event-free survival was higher in adherent patients versus nonadherent patients (76.6 vs 59.8%, p = 0.011).

A patient record review of CML patients from Brazil, France, Italy, Spain and Russia also revealed that higher adherence rates were related to achieving therapeutic milestones [19]. At the time of writing there were not yet any studies published that investigated the relationship to second-line TKIs and clinical response. Nonetheless, it is very likely that adherence will be found to influence response in these patient groups; in particular as nonadherent patients have been found to have more and longer hospital inpatient stays, which is likely to be an indicator of suboptimal response [30].

The Stop Imatinib trial evaluated the effect of discontinuing imatinib therapy, which could be seen as analogous to a prolonged period of complete nonadherence [31]. The study included 100 patients, across 19 French institutions, all of whom had maintained complete molecular response for at least 2 years. Their imatinib treatment was discontinued and the patients were closely monitored for signs of relapse. Of 69 patients whom had been followed up for a minimum of 12 months at the time of the publication, 42 (61%) patients relapsed, mostly within 6 months. All the patients who had relapsed responded well to imatinib after resumption of therapy [31]. In addition, a small observation study of 23 Korean CML patients who had achieved either CCyR or complete molecular response at the point of discontinuation (mainly due to economic reasons) found that after resumption of imatinib therapy all patients, but one who progressed and two who maintained their molecular remission, achieved their previous best levels of clinical response [32]. Although these studies suggest that imatinib therapy may be discontinued in some patients for longer periods without relapse of the disease; it is still too early to say whether in the future it will be possible to consider TKI therapies a 'cure' for CML and discontinuation of TKI therapy should only be done in a controlled setting and should be closely monitored by the healthcare team.

Finally, nonadherence can constitute a significant bias in clinical trials evaluating the effect of therapeutic agents and it has been argued that adherence rates should therefore always be monitored, controlled during analysis and reported in publications [33]. If the patient has a low level of adherence in the trial this could lead to the selection of an inappropriately high drug dose and potential underestimation of dose-related toxicities. Conversely, if the adherence rate is higher in a clinical trial setting compared with normal care, the treatment may not be as effective when released on the market as the trial results suggested.

Quality of life

There is mixed evidence in terms of the influence of quality of life on adherence behaviors. Patients with lower adherence rates may experience higher quality of life if they experience fewer side effects. Noens *et al.* reported that higher self-reported functional status and quality of life had a negative influence on adherence rates in multivariate analysis, although they did not find statistically significant associations between adverse events or disease symptoms with adherence rate (using pill count) during univariate testing [20]. Marin *et al.*, on the other hand, found that patients who were nonadherent (≤90 of doses taken) reported more low-grade adverse events, including asthenia, nausea, muscle cramps and bone or joint pains [23]. Overall quality of life as measured with the FACT-G questionnaire was unrelated to adherence. However, patients who scored in the lowest quartile of the physical well-being subscale of the FACT-G had a lower adherence rate than the others (88 vs 95% respectively, $p = 0.05$). It is not surprising that some trials do not find association between adverse events and adherence rates as patients who are adherent also tend to experience side effects. However, qualitative studies into patients' reasons for not taking imatinib have found that patients often state side effects as the main reason for missing doses [34]. This suggests that adherence rates may not be influenced by whether or not the patient experiences side effects *per se*, but by how the patient copes with the adverse events.

Economic impact

Darkow *et al.* used MPR as a proxy measure of adherence based on retrospective electronic health claims data for 267 CML patients in the USA [16]. The total days' supply of all imatinib fills was divided by the 365 days follow-up period (over supply was truncated at 100%). The mean MPR was 77.7% (SD 27.5%). A total of 46% of patients had an MPR of less than 90%, 20% of patients had an MPR of less than 50% and 30.7% of patients had treatment interruptions of at least 30 consecutive days during the follow-up period. Women had lower MPR and were more likely than men to have treatment interruptions. In addition, increased pill burden (number of different drugs prescribed) and initiation of an imatinib dose of 600 mg or higher was also associated with decreased MPR. Reduced MPR was related to more and longer inpatient hospital stays, increased number of hospital visits and increased healthcare and medical costs. A 10% point difference in healthcare costs, excluding the cost of imatinib, predicted a 15% difference in medical costs [35].

These results were recently supported by two other studies conducted using data from US health claims databases. Wu *et al.* found that 40.9% of patients in their sample (n = 592) had an imatinib MPR less than 85% and regression models demonstrated a 283% increase in medical costs, excluding the cost of imatinib, between patients with MPR less than 85% versus patients with MPR greater than or equal to 85% [17]. Demographics such as age, gender and pill burden were not found to be associated with adherence [23]. Halpern *et al.* found that 55.6% of 374 patients in the first year of follow-up and 61.8% of patients in the second year had imatinib MPR of less than 90% and that nonadherent patients had more and longer inpatient stays and higher healthcare costs and resource utilization [21].

Similar results have been found using claims data of patients prescribed either dasatinib or nilotinib as second line. Wu *et al.* included 452 patients prescribed dasatinib and 69 patients prescribed nilotinib and found a higher mean adherence rate in nilotinib patients (MPR 75%), whilst dasatinib patients, having lower rates of adherence (69%), incurred more and longer hospital stays and higher healthcare costs [36]. However, another study found that patients from the USA who were prescribed dasatinib had higher adherence rates than nilotinib patients [37].

Predictors of nonadherence & patients' reasons for missing doses

There is no typical nonadherent CML patient and to find consistent patient-related predictors of nonadherence across studies has not been possible, albeit that within studies certain demographics or treatment-related variables are often found to influence adherence rates **(Table 2)**. In addition, patients enrolled in clinical trials have been found to have higher adherence rates [18]. In terms of imatinib, patients who have been initiated on a dose greater than 400 mg/day are often found to have lower adherence rates than patients started on a dose less than or equal to 400 mg/day [16,17,20]; although there are examples where dose has been unrelated to adherence rates [18]. In some studies the number of co-therapies prescribed has been related to adherence [16], whilst others have found the opposite [20] and yet other studies have not found a relationship between pill burden and adherence rates [17–19]. Comorbidities have also been found to influence adherence rates [28], although again the picture is complicated by others reporting contradictory results [17,19]. Low-grade adverse events have been found to negatively affect adherence rates (as grade III–IV adverse events are likely to lead to discontinuation of TKI treatment by the prescribing physician) [23]; and although another study found that patients who were nonadherent were more likely to report higher functional status and quality of life, in-depth interviews with patients that were conducted in relation to the aforementioned Marin *et al.* trial, revealed that adverse events were the most common reason patients gave for intentionally missing doses of imatinib [34].

The interviews also revealed that patients expressed both intentional and unintentional reasons for missing doses, which at times overlapped. What was surprising, however, was that patients did not appreciate the consequences of missing relatively few doses; a belief that seemed to have been reinforced in patients by healthcare professionals downplaying the impact of nonadherence [34]. Nonetheless, it should be pointed out that the interviews were conducted before reports of the clinical effect of nonadherence had been published. It is therefore possible that healthcare providers and patients today have a better understanding of the consequences of nonadherence.

How to identify & measure nonadherence

How then can we identify nonadherent patients if demographics and other potential predictive factors are unreliable? Using predictive measurements to identify patients likely to be nonadherent, with the aim of focusing interventions on these patients, is one approach with inherent limitations. In particular, the fact that predictive measurements are never perfect and there will always be adherent patients wrongly predicted to be nonadherent and nonadherent patients wrongly identified as adherent.

A way forward would be to use diagnostic measurements to monitor adherence rates. We know, for example, that adherence is closely linked to response; thus if a patient has suboptimal response the first thing to consider is whether the patient is taking the medication as prescribed.

Other methods to measure adherence are to monitor patient records; including pharmacy

refill records and health claims data, and pill count where the patient is asked to bring in any leftover doses to clinic. Imatinib through plasma levels have been found to be related to adherence rates in some studies. However, this method is sensitive to so called "white coat adherence" where the patient adheres perfectly, or even overdoses, in the days before an appointment. When funding allows, electronic monitoring can be recommended as it is considered the most reliable and valid measure of adherence currently available.

The most straightforward way to measure adherence is self report, basically asking the patient to report whether s/he has missed doses, which if done in the right way can be both reliable and valid. Self report is also the only way that we can find out reasons why doses have been missed, whether it was done intentionally or unintentionally, which is paramount if we are to intervene to reduce nonadherence and support patients in managing their treatment.

All adherence measurements have their advantages and limitations. Arguably no one measurement method can be recommended overall, rather it is important to tailor the adherence measurements according to the objectives of the assessment, such as clinical versus research purposes, and it may be worthwhile to use multiple measures of nonadherence to reduce measurement error [38].

Interventions for improvement

There were no studies identified in this review that specifically reported adherence-enhancing interventions for CML patients prescribed TKI treatment. However, the survey of patient records reported by Guilhot *et al.* found that patients within France, Italy and Spain who received adherence counseling by either a nurse or a hematologist and patients who attended clinics at institutions that had established protocols to address adherence issues had higher adherence rates [19]. This suggests that supportive advice and improved communication regarding adherence issues between patients and healthcare providers may support patients' treatment adherence. It may also be helpful if CML patients were seen during dedicated CML clinics where they would have access to healthcare providers specializing in CML. However, there is little data available on what the effect of attending dedicated CML clinics has on patients' adherence rates, quality of life and clinical response and further research is needed to assess their usefulness.

Side effects can also be a cause for nonadherence, in particular intentional nonadherence when the patient decides to miss doses; thus managing adverse events is likely to be a key factor in supporting patients' adherence. Dose adaptation is an important consideration when managing adverse events and toxicity. It is essential, however, that this is done in concordance with the treating physician and under close monitoring of clinical parameters to avoid patients adapting doses without the knowledge of their doctor.

Improving communication should not be done solely with the aim of increasing adherence *per se*, but also to increase patient autonomy and encourage patient involvement in making decisions about their treatment [39]. All CML patients have a right not to adhere if they do not want to or to alter treatment to better suit their lifestyle. Nonetheless, the aim should be that the healthcare provider can provide the relevant information and support to allow the patient to make an informed decision about their treatment. In addition, different patients may want to have different levels of involvement in making decisions regarding their treatment. For example, research has shown that patients of younger age and of higher social class may prefer a greater involvement in treatment decisions than others [40]. Patients should therefore be allowed to defer treatment decisions to the healthcare provider if desired. There is also no consistent evidence that written information, such as patient information leaflets, increase patient satisfaction or adherence to treatment [41].

Routine monitoring of adherence rates would be a key component to monitor the ongoing effectiveness of adherence services and interventions. However, routine monitoring may feel intrusive to patients and could thus have an adverse rather than a positive effect on the patients' general wellbeing and adherence rates. Careful consideration therefore is necessary before implementing such monitoring in clinical practice; in particular, with regards to how such information should be used and to what extent patients should be involved in the process.

It may be possible to involve patients in the process of routine monitoring and use this to engage in communication about adherence

issues. One way to do this could be to use MEMS monitoring with the patients' knowledge. The adherence data collected could be shown to the patient and reasons for missed doses could be discussed in clinic and the causes could be addressed. Indeed, MEMS feedback has previously been used as an adherence-enhancing intervention in other illness groups, such as HIV and diabetes [42,43].

Treatment nonadherence is evidently a multifaceted issue and, therefore, focussing interventions on improving the system as a whole to support all patients may provide a better resultant influence on the way patients manage their treatment. This should include health services to address adverse event, access to medication, patient–healthcare provider communication and provision of adherence aids, such as dosing boxes and alarms.

Conclusion

This review has given an overview of the current understanding of the extent, consequences and reasons for CML patients' nonadherence to their prescribed treatment regimen. Nonadherence is evidently extensive in this patient group and the consequences are severe, both in terms of reduced clinical response for individual patients and in terms of the associated healthcare cost. It is less clear how we can identify nonadherent patients in practice and how to best address the issues that lead to nonadherence, although managing side effects, providing supportive advice regarding treatment management and improved communication between healthcare providers and patients are likely to be key factors to address in order to improve adherence to a TKI regimen.

Future perspective

The past 5 years have seen an expanding body of evidence and understanding of the effects of treatment adherence in the management of CML, and healthcare providers have accepted that nonadherence is common amongst CML patients who are prescribed oral TKIs. This may have already influenced clinical practice across the world so that closer attention is paid to patients' adherence and services are being developed to support patients. Nonetheless, nonadherence is a multifaceted challenge and we need to understand the causes of both intentional and unintentional nonadherence and to address these appropriately. The research focus in the coming years is likely to further our understanding of the causes and consequences of nonadherence to second- and third-line TKIs, as well as to develop and evaluate adherence measurements and interventions. The challenge is to develop healthcare systems that support patients in taking their treatments optimally, whilst simultaneously allowing autonomy and encouraging patient involvement in treatment decisions.

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