Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org

Review article

Importance of adherence to BCR-ABL tyrosine-kinase inhibitors in the treatment of chronic myeloid leukemia

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ARTICLE INFO

Article history:
Received 10 May 2013
Accepted 19 August 2013

Keywords:
Patient compliance
Therapeutics
Leukemia, chronic myeloid
BCR-ABL positive

ABSTRACT

Treatment of chronic myeloid leukemia with BCR-ABL tyrosine kinase inhibitors requires full adherence in order to maximize the likelihood of achieving optimal responses, and to minimize healthcare costs. In this article, we review some of the methods available for assessing compliance, the main consequences of nonadherence on treatment outcomes, major factors commonly associated with poor compliance, a few successful measures for improving adherence and the most accepted recommendations for proactively managing adverse events.

Introduction

Extraordinary scientific progress made in the field of chronic myeloid leukemia (CML) led to the development of orally available tyrosine kinase inhibitors (TKIs), dramatically improving treatment results for patients with chronic-phase CML (CP-CML).[1,2] Imatinib (Gleevec®; Novartis, Basel, Switzerland) was the first TKI to obtain market authorization for the treatment of newly diagnosed patients; this was subsequently followed by the approval of dasatinib (Sprycel®; Bristol-Myers Squibb, Princeton, NJ, USA), and nilotinib (Tasigna®; Novartis, Basel, Switzerland), a highly potent second-generation TKI, adding the option of a second-line TKI therapy following imatinib resistance or intolerance.[1,3]

Despite these exciting new possibilities improving therapeutic outcomes in adults with CP-CML, a significant proportion of patients fail to take full advantage of the benefits of TKI therapy only because of poor adherence,

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1516-8484/$ - see front matter © 2014 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.
DOI: 10.5581/1516-8484.20140014

determined by socioeconomic factors and factors related to the healthcare system, the patient, the drug, and the disease. While oral agents engineered for cancer treatment are far more convenient for patients, and generally yield remarkable time and cost savings to the healthcare system, the optimization of treatment results eventually relies on adequate patient compliance to the prescribed therapy. This scenario highlights the importance of measuring, monitoring, and ensuring effective adherence to TKI treatment regimens, allowing CML patients to achieve the best possible outcomes.[1,4-6]

Due to the growing relevance of this theme, a review of the literature in PubMed was performed, using the keywords 'adherence', and 'CML treatment'.

Measuring adherence

Cancer patients are usually regarded as highly driven by the severity of their disease, and oncologists tend to presume that the patients will take the oral antineoplastic agents as prescribed. Nonetheless, nonadherence is a relatively common event during long-term treatment with TKIs, and as this phenomenon has been associated with worse outcomes, healthcare professionals should exclude this possibility before deciding on switching to next-line treatment in cases of unsatisfactory response. Several different methods are available to measure adherence to oral agents, even though all have flaws and limitations.[7-9]

Self-reporting, in which patients are requested to recollect how reliably they complied with their treatment regimen, has been criticized as too subjective, with a propensity for patients to over-report rates of adherence. In addition, some studies have surprisingly showed that adherent patients may sometimes report nonadherence. Although prospective patient diaries may also yield biased information regarding treatment compliance, they may be less influenced by recall bias on account of the supposed documentation after each dose taken.[8-11]

Pill counting, in which patients are required to return untaken pills for the calculation of missed doses, has been demonstrated to grossly overestimate adherence, mainly due to dumping of unused pills. Moreover, this method fails to provide information about compliance with dosing schedule. Pill counting is particularly subjected to bias; it becomes even less accurate when patients know that their pills will be counted.[8,9,12,13]

Measurement of serum drug levels is a method commonly thought to provide a less biased estimation of adherence. However, variations in individual pharmacokinetics, such as rates of drug absorption, distribution, metabolism, interactions and excretion, can significantly influence the assessment of adherence. Furthermore, non-adherent patients can still manipulate test results by taking extra doses of drug just before the exam, thereby giving the false impression that the patient is taking the drug correctly. Lastly, the costs of this test may be prohibitive for routine use outside the clinical research setting.[8,9]

Microelectronic Monitoring System (MEMS) is a newer method for assessing adherence that consists of an electronic device fitted into the cap of a regular looking drug bottle that electronically records every time the bottle cap is removed, and provides a computerized list of dates and times of bottle openings for several weeks. Because the system generates a good estimation of the number of doses taken daily, the number of missed or extra doses, and the dosing intervals, MEMS is often regarded as the gold standard to measure adherence; however, receiving a different bottle from the usual, as well as patient's awareness of the system itself, may both be sources of bias. Besides, the act of opening a pill container does not necessarily imply that the patient actually took the drug as prescribed. MEMS is also significantly expensive, and hence used mainly for clinical research, rather than for large-scale monitoring of patient populations.[5,8,9]

Pharmacy and medical records are also used to evaluate treatment compliance, possibly offering the most reliable estimation of actual drug use in large populations over a long period of time. With the Medication Possession Ratio method, adherence can be calculated as the amount of doses available to a subject in a given period, divided by the number of doses required for achieving full adherence to the treatment regimen during the same period of time. Although pharmacy or medical records avoid both recall bias and patient manipulation for social desirability, no information about dosing interval and schedule is provided since it is possible to miss doses, double up on pills, or even not take the drug at all, and still get prescriptions refilled on time.[8,9]

All methods present advantages and disadvantages that should be taken into account and the association of more than one method might improve the evaluation of treatment adherence. Therefore, even though measuring adherence is an essential step to ensure the highest likelihood of getting optimal results from TKI therapy for CP-CML patients, clinicians and the multidisciplinary team should be well aware of the strengths and weaknesses of each of the available methods used for this purpose and extreme caution should be exercised with the interpretation of data collected on treatment adherence.

Nonadherence and treatment outcomes

In general, it has been estimated that noncompliance with TKI therapy increases up to three times the risk for poor treatment outcomes of CP-CML patients.[7]

In a study using MEMS to measure adherence levels during a three-month period in 87 consecutive CP-CML patients who had received imatinib as first-line therapy, it was demonstrated that treatment adherence is a critical factor for achieving and maintaining molecular response in this group of patients. While median adherence was very high (98%) in this study, the probability of achieving major and complete molecular responses was significantly better in patients with more than 90% of treatment adherence (28.4% *vs*. 94.5%; p-value < 0.001, and 0% *vs*. 43.8%; p-value = 0.002, respectively). In multivariate analysis, adherence was the only independent predictor for achieving complete molecular response.[5]

In a subsequent study, the probability of loss of complete cytogenetic response at two years was significantly higher in patients with an adherence rate of 85% or less (p-value = 0.0001). An adherence rate of 85% or less (relative risk = 27.8; p-value = 0.002), and never having achieved a major molecular response (relative risk = 14.9; p-value = 0.01) were the only

independent predictors for loss of complete cytogenetic response and imatinib failure in the multivariate analysis.[14]

The Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study evaluated 169 CML patients using imatinib from 34 Belgium centers over a 90-day period. In this study, only 14.2% of all patients were found to be perfectly adherent to imatinib, while 71% took less than the prescribed dose and 14.8% took more. Patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23.2%; standard deviation = 23.8) than did those with optimal response (7.3%; standard deviation = 19.3; *p*-value = 0.005).[7]

Recently, several other studies assessed adherence to imatinib in the treatment of CML. In a retrospective analysis performed in India, using the Glivec International Patient Assistance Program (GIPAP) database, 29.6% of patients were found not completely adherent to imatinib and, in a multivariate analysis, nonadherence was the only factor significantly affecting event-free survival.[15] On the other hand, few studies have evaluated adherence to second-line BCR-ABL TKIs. In a retrospective study published in 2012, patients receiving second-line nilotinib had poorer adherence, compared to patients taking dasatinib (100 mg once daily). No correlation was found between adherence and treatment response.[16]

In summary, nonadherence to TKI therapy in CML was correlated with poor therapeutic outcomes and increase of healthcare costs with these patients.[17,18]

Factors affecting treatment adherence

Adherence to oral anticancer treatment is a complex issue and a number of factors have been shown to predict nonadherence. The presence of depression, disbelief in the benefits of the drug, having to take other drugs for comorbidities, chronicity of disease, and length of treatment, are all important factors that may contribute to nonadherence in cancer patients.[1,4] In addition, TKIs Adverse Events (AEs), clinicians' and site staff experience, practice behavior, and setting, and patients' level of knowledge, were also all shown to have an impact on adherence.[7] Furthermore, illiteracy, poor education, and lower cognitive level are factors that can restrict patients' comprehension of the instructions given on treatment schedules and effects.[6]

The unavailability of appropriate home support is an additional source of increased likelihood of nonadherence, as changes in every-day activities can escalate tension with family and friends.[19] Among the socioeconomic factors, although low economic status has not been considered an independent predictor of adherence, this status may induce patients to favor family needs over the best treatment available. In that regard, cancer treatment, particularly in elderly, usually demands substantial effort on the part of patients and caregivers, including many sacrifices in terms of economic resources to meet the cost of therapy.[4] It has been shown that economic factors can indeed influence cancer patients' decisions about their treatment,[1,20] with those taking oral biologic agents being more inclined to restrict or discontinue doses when faced with situations of economic deprivation.[1,20]

Eliasson et al. found that longer duration of treatment, and having already achieved the expected therapeutic response, also tend to reduce adherence. Additionally, they explained that unintentional nonadherence generally refers to those situations when the patient may have wanted to take the drug but was unable to, either because of a personal cause, such as forgetting, or due to an external one, such as prescribing error, whereas intentional nonadherence refers to those situations in which the patient deliberately decides not to take the drugs as prescribed.[19]

More recently, the Italian Group for Adult Hematologic Diseases (GIMEMA) evaluated factors associated with adherence behavior in 413 CML patients receiving long-term therapy with imatinib. While 53% of patients reported optimal adherence, univariate analysis showed that concomitant drug burden and shorter time since achieving complete cytogenetic response were associated with better adherence (*p*-value = 0.019). In the multivariate analysis, higher level of social support, satisfaction with information received about the impact of disease and therapy, and concomitant drug burden were correlated with better adherence (*p*-value = 0.001, *p*-value = 0.001 and *p*-value = 0.006, respectively).[21]

Improving adherence

Although adequate compliance with BCR-ABL TKIs is critical to maximize treatment effectiveness and reduce the economic burden of disease among CML patients,[18,21] many patients were found to ignore the fact that missing even a few doses of TKI therapy was likely to affect their response to treatment.[1,11,18,19,22-24] A meta-analysis of adherence-enhancing interventions found the highest impact for interventions combining educational and behavioral strategies versus each strategy alone.[7] Therefore, chronic treatment with oral TKIs demands the use of new concepts and guidelines by healthcare professionals, in order to manage and follow-up CML patients. Improving treatment adherence for these patients will require appropriate access to information, an experienced multidisciplinary team, and continuous monitoring. Increased accessibility to pharmacists, behavioral specialists, and social workers, will enable the identification of causes for nonadherence,[9,11,19] and the knowledge of these causes will allow the development of an action plan consistent with the needs of each individual patient. In this process, patient education about the disease and the treatment, as well as about prompt reporting of side effects, is indispensable to improve adherence.[1,22]

Managing adverse events

Therapy with BCR-ABL TKIs for CP-CML is generally well tolerated, although not completely free of side effects,[3] and the occurrence of these side effects is associated with lower adherence.[5] Recently updated clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) provided specific recommendations for the management of AEs associated with imatinib, nilotinib, and dasatinib, in order to avoid compromising the clinical efficacy of these TKIs. Generally, grade 3/4 AEs are managed by dose interruption,

followed by resumption of treatment at a reduced dose after resolution of toxicity.[25] Time to recovery for each individual patient is used to guide dosing decisions. Common mild or moderate AEs are managed with specific treatments or supportive care.[1]

Myelosuppression is observed in a significant proportion of CML patients treated with TKIs, especially among those with more advanced disease, and in those receiving dasatinib or nilotinib after previous imatinib treatment.[3,22,26] In addition, a low incidence of bleeding events, usually related to the development of thrombocytopenia, has been reported with dasatinib.[27] Thus, CML patients receiving TKI therapy should be educated to identify and immediately report fever, particularly in conjunction with infection, as well as easy bruising.[22,27] Blood counts should be monitored weekly in the first month of treatment, monthly during Months 2 and 3, and at every 3 months thereafter. Cytopenias are primarily managed by dose modification or interruption, and prescribing information for each BCR-ABL TKI describes the appropriate adjustments according to the intensity of these AEs.[22] The use of growth factors, such as granulocyte colony-stimulating factor and recombinant human erythropoietin, has shown to allow continuous administration of TKI therapy without jeopardizing its antileukemic effect.[3] Nonetheless, growth factors are not approved in this setting and recent guidelines do not support the use of erythropoietic-stimulating agents in myeloid malignancies.[22]

Peripheral edema is one of the most common AEs associated with BCR-ABL TKIs. Periorbital edema can be improved by elevating the head during sleep, and topical hydrocortisone or phenylephrine.[3,22] Close electrolyte monitoring, restricted salt intake, administration of low-dose loop diuretics such as furosemide, and eventual supplementation of potassium and magnesium, have all proved to be helpful in the management of moderate edema. More severe cases may require treatment interruption and, in some cases, surgery.[3]

Pleural effusion is an extremely rare complication of TKI therapy for CML.[3] However, all patients, particularly those with risk factors, should be educated about shortness of breath, and should be monitored closely for symptoms suggestive of fluid retention, including regular assessment of body weight, heart- and lung-associated symptoms, and peripheral tissue tone. Rapid weight gain should prompt immediate investigation.[22, 27] Although the administration of pulse steroids, in addition to treatment interruption, has been associated with faster resolution of the pleural effusion, part of the beneficial effect might be related to the sudden decrease in TKI levels. Large recurrent effusions may require thoracentesis, a temporary pleuroperitoneal shunt, and/or pleurodesis. After resolution of the effusion, therapy usually can be resumed at a reduced dose.[3]

Skin toxicity, generally characterized by maculopapular rash, has been reported during TKI therapy in CML patients. Symptoms are usually mild and self-limiting, allowing treatment continuation.[3,22] For the minority of patients requiring interventions, antihistamines, short courses of steroids, and topical triamcinolone acetonide ointment may hasten the palliation of symptoms.[26] Rare cases of Stevens-Johnson syndrome mandates immediate interruption of TKI treatment and administration of systemic steroid therapy.[3]

A low proportion of CML patients can experience gastrointestinal AEs during TKI therapy. Usually, there is a continuous increase in the frequency of bowel movements during the initial treatment phase of treatment, rarely progressing to diarrhea symptoms. Bowel function tends to return to normal after a few weeks.[26] Reduction in gastrointestinal symptoms has been associated with the ingestion of BCR-ABL TKIs with water and large meals, except for nilotinib, which requires fasting for its administration.[22] Although seldom necessary, anti-emetic and anti-diarrheal drugs can be used for the management of gastrointestinal AEs, permitting treatment continuation without reductions or interruptions.[26]

Altered levels of liver enzymes have been frequently reported in CML patients treated with TKIs, usually requiring measurement of liver function at baseline, every week for the first month and every 3 months thereafter. Patients should be advised to refrain from drinking alcohol or taking any hepatotoxic drug. Mild abnormalities generally allow continuation of TKI therapy under careful monitoring. Treatment should be interrupted in case of grade 3/4 toxicity, but dose can be resumed at the same level after improvement of liver function. Treatment should be permanently discontinued in case of recurrent serious toxicity.[3] Pancreatic abnormalities have been reported during nilotinib therapy; therefore, caution is advised when using nilotinib in patients with a history of pancreatitis. Lipase levels should be monitored in these cases.[22]

Muscular spasms and muscle pain have also been associated with TKI therapy. Relief of cramps can be obtained with calcium and magnesium supplements or quinine. Non-steroidal anti-inflammatory drugs may help to relieve mild pain in patients with adequate platelet counts and no prior gastrointestinal bleeding.[22,26]

Cardiotoxicity is an infrequent, but potentially life-threatening complication of BCR-ABL TKIs. Since abnormalities in mineral metabolism, including hypophosphatemia, hypokalemia, hyperkalemia, hyponatremia and hypocalcemia, have been reported with all BCR-ABL TKIs, electrolyte levels should be corrected before therapy and periodically monitored during therapy, thus preventing negative effects on cardiac function. In addition, strong CYP3A4 inhibitors should be used with caution during imatinib treatment, and should be avoided during nilotinib and dasatinib therapy.[22] The management of cardiac AEs generally includes treatment discontinuation, echocardiographic monitoring, and aggressive therapy with diuretics, angiotensin-converting enzyme inhibitors, and beta blockers.[3]

Conclusion

A highly specialized and well-trained multidisciplinary team that is capable of gaining the trust of patients and improving long-term treatment adherence is of utmost importance for the treatment of CP-CML patients in the modern era. Collecting

specific information about factors that affect treatment adherence is necessary, and establishing an individualized approach to these patients is strongly advised.

Although BCR-ABL TKIs have revolutionized the treatment of CP-CML, monitoring and ensuring adherence to these agents is an essential step for achieving optimal responses and for decreasing the economic burden of the disease. Patient education programs, devices with reminder function, strong family support, a solid patient-physician relationship, periodic telephone counseling, and proactive management of AEs, are all initiatives that may help to increase compliance to treatment, and should therefore be considered for all patients receiving BCR-ABL TKIs for the treatment of CP-CML.

Conflicts of interest

The translation of this article was funded by Bristol-Myers Squibb.

Acknowledgments

Professional medical writing and editorial assistance was provided by Synecticomm and was funded by Bristol-Myers Squibb.

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