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Burden of Tyrosine Kinase Inhibitor Failure in Patients with Chronic Myeloid Leukemia

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Abstract

Tyrosine kinase inhibitors (TKIs) have been extremely effective at inducing remissions and slowing down the progression of chronic myeloid leukemia (CML) resulting in a significant reduction in morbidity and mortality. Most patients with CML must remain on TKIs indefinitely and many experience resistance or intolerance to TKIs requiring a switch to a second-line TKI, third-line TKI or more. The purpose of the current review is to examine the underlying factors and subsequent economic and quality of life burdens associated with TKI failure. We discuss the definitions and rates of TKI failure in CML and the extent to which mutations and non-adherence are associated with TKI failure. We also review the few studies that have examined economic and patient outcomes associated with TKI failure and we suggest avenues for future research examining the consequences of TKI failure.

Keywords: Tyrosine kinase inhibitors; Chronic myeloid leukemia; Resistance; Burden

Introduction

In 2012, chronic myeloid leukemia (CML) accounted for 15% to 20% of newly diagnosed cases of adult leukemia in the U.S. [1]. In 2014, there will be an estimated incidence of 5,980 new cases (men=3,130; women=2,850) and a total of 810 deaths (men=550; women=260) due to CML [2]. Tyrosine kinase inhibitors (TKIs), the primary therapy used to manage CML, has the following treatment goals: (1) to induce complete clinical remissions; (2) to prevent the progression from chronic phase (CP) to any other phase (e.g., accelerated or blast); (3) to reduce the risk of death from disease; and (4) to increase the quality of life (QoL) of CML patients [3]. TKI therapy has resulted in a 2% annual all-cause mortality rate among CML patients, a major decrease from the historical rate of 10% to 20% [2]; the estimated 10-year survival rate has increased from 20% to 80% [4]. These gains in survival are only realized if CML patients remain on TKIs long-term. However, over the course of therapy, many patients experience resistance or intolerance to TKIs, requiring a switch to a second- or third-line TKI. TKI failure is expected to be associated with a substantial economic and humanistic burden of illness. In the current paper, we review the underlying factors and subsequent economic, and QoL burden of TKI failure.

TKI Failure: Definitions and Rates

Failure is often used to mean that continuing a specific treatment is no longer appropriate because a favorable outcome is unlikely and includes both resistance and intolerance. Although several definitions of resistance to TKIs have been used, the 2014 National Comprehensive Cancer Network (NCCN) guidelines [5] define primary resistance as the failure to achieve a response by a specific time point. Primary hematologic resistance to TKIs is defined as the failure to achieve hematologic remission within 3 to 6 months of treatment initiation. Primary cytogenetic resistance to imatinibis defined as the failure to achieve any level of cytogenetic response (CyR) at 6 months, major cytogenetic response (MCyR) at 12 months, or complete cytogenetic response (CCyR) at 18 months [5]. The 2013 European LeukemiaNet (ELN) guidelines define failure as less than CyR at 3 months, MCyR at 6 months, and CCyR from 12 months onwards [6]. Secondary resistance refers to a loss of therapeutic effect and disease progression while continuing on a TKI regimen that had previously been effective. The 2014 NCCN [5] and 2013 European LeukemiaNet guidelines [6] both stress the percentage of *BCR-ABL1* transcript as a marker of treatment response. Treatment could be reevaluated if *BCR-ABL1* transcript levels are greater than 10% at 3 and 6 months.

Despite the effectiveness of imatinib, the most common TKI used in first-line therapy, up to 40% of patients with CP CML will become resistant to imatinib [7-9]. For example, in the pivotal International Randomized Study of Interferon versus STI571 (IRIS) trial, approximately 30% of CML patients did not achieve CCyR after 12 months [10,11]; at 18 months, 24% of patients had primary resistance [11]. Long-term follow-up analysis of the IRIS trial reported that secondary resistance occurred in 24% of patients after 5 years [12]. Results from additional studies suggest that the failure rate of imatinib could be as high as 45% at 24 months [13] or 26% after a median follow-up of 38 months [9]. Rates of resistance to first-line therapy with nilotinib and dasatinib are lower than that of imatinib, but are still substantial [14,15]. At 12 months, the rates of resistance to nilotinib and dasatinib are 16% and 18%, respectively [14,15]. At 24 months, the rates increase to 23% for nilotinib and 26% for dasatinib [16]. With second-line therapy, 37% to 52% of patients failed to have a response to therapy [17-19]. Many patients who were not initially resistant lost their response by 2 years [17,19].

Intolerance to TKI therapy, another type of failure, is one of the most common reasons for discontinuation. However, reported rates of intolerance are not consistent across studies, possibly because there is currently not an agreed upon definition of intolerance. Data from

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clinical trials have suggested that intolerance to TKI therapy occurs in less than 5% of patients taking imatinib [20,21]. However, a real-world study found imatinib intolerance in 30% of patients [22]. With long-term therapies like TKIs, a patient's QoL may be a better tool to gauge therapy intolerance.

Factors associated with TKI failure

Mutations: Several mechanisms have been associated with TKI resistance, but the best-characterized are the BCR-ABL1 kinase domain (BCR-ABL1 KD) mutations [23]. Mutations are rare in newly diagnosed patients in CP and become significantly more prevalent in CP disease that develops resistance, as well as advanced-phase disease [24-26]. Twelve to 63% of patients who develop resistance to imatinib have the BCR-ABL1 KD mutation [27]. Most patients with secondary resistance developed mutations during imatinib treatment [28]. Patients with existing mutations are more likely to develop additional mutations. Sequential treatment with different TKIs is associated with the emergence of new mutations [29]. During second-line TKI treatment (dasatinib or nilotinib), approximately 14% to 33% of patients develop new BCR-ABL1 mutations [28]. The appearance of multiple mutations is associated with poorer prognosis [23]. Up to 40% of patients resistant to second-line TKIs involves the T315I mutation [30,31], which is resistant to all TKIs except ponatinib [32]. The reported median survival of patients with the T315I mutation is approximately 22 months after the mutation is detected [33].

Medication non-adherence: Approximately 30% of CML patients taking TKIs are non-adherent [34,35]. This is not surprising as adherence to oral anticancer therapy has been reported as ranging from 16% to 100% [36]. TKI non-adherence is related to an increased risk of suboptimal response, disease progression, higher healthcare costs, and increased mortality [34,37,38]. Marin et al. found that imatinib adherence was one of only two variables that uniquely predicted whether patients achieved a major molecular response [38]. A follow-up to this study found that imatinib's adherence rate was an independent predictor for loss of CCyR and the discontinuation of imatinib therapy [37]. Patients with adherence rates of 85% or less were significantly more likely to lose CCyR at 2 years and less likely to remain on imatinib than patients with an adherence rate greater than 85%. A retrospective cohort study conducted in Taiwan found that better long-term adherence to imatinib was associated with better clinical outcomes [39].

With respect to second-generation TKIs, one study found patients treated with nilotinib had significantly higher adherence rates compared to patients treated with dasatinib, regardless of dasatinib dose (100 mg/day and 140 mg/day) [40]. Adherence was found to be worse in dasatinib patients compared to nilotinib patients [41], perhaps because adverse events (AE) are more common with dasatinib than nilotinib. However, another retrospective claims database study reported that patients taking second-line nilotinib were almost two times more likely to have poor adherence than patients taking second-line dasatinib at 100 mg/day [42]. This difference between the two studies could be due to their methodology; the former stratified by dasatinib dosage, the latter by age.

Given the substantial impact of non-adherence, a number of studies have identified covariates associated with non-adherence to TKIs. Adherence has been found to be worse as the number of medications increased, worse among women, worse in patients receiving a higher initial dose of imatinib, and worse in patients with high cancer complexity [43]. Non-adherence has also been linked to the treating physicians' experience, practice patterns, and practice environment [34]. Furthermore, an attitudinal study of CML patients found that the most common reasons for non-adherence were simply forgetting to take the dose and to avoid experiencing side effects [44].

Suboptimal response: A suboptimal response, referred to as a warning response by the 2013 European Leukemia Net guidelines [6], is defined as one that does not meet the criteria for failure (resistance) or for an adequate response [5]. Patients with a suboptimal response have a greater risk of disease progression compared with optimal responders [12,45,46]. Studies have found that a suboptimal response at the beginning of therapy is more prognostic than a suboptimal response later in treatment. For instance, patients with a suboptimal response at 6 months have similar outcomes including overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) as patients who experienced TKI failure. In contrast, there were no significant differences between patients with a suboptimal response at 18 months and those with an optimal response [47,48].

Lack of early response: Studies have found that achieving CCyR at 12 months after the start of TKI therapy is significantly related to better patient outcomes [9,49]. CyR at 3 months significantly predicts 3-year OS, regardless of the first-line therapy regimen that patients had received [50]. Patients with a poor molecular response early in first-line therapy are more likely to experience significantly shorter duration of PFS [51], worse OS [52], and greater probability of TKI resistance [53]. Marin et al. found molecular response at 3, 6, or 12 months from the start of imatinib therapy was significantly associated with OS, PFS, and CyR 8 years later [52]. The values at month 3 were the strongest predictors of patient outcomes [52]. Similarly, Jain et al. found that patients with a better molecular response at 3 months had longer EFS, failure-free survival, and OS, regardless of whether the first-line treatment was imatinib, nolotinib, or dastinib [50]. Consequently, patients' cytogenetic and molecular response to first-line therapy during the first year, particularly at month 3, is significantly related to long-term outcomes. Patients with poor responses are more likely to fail first-line therapy. It is critical that patients are routinely tested and monitored per guidelines to insure the detection of resistance or suboptimal response to first-line therapy.

First-line resistance leads to subsequent resistance: There are a number of factors associated with how well a patient responds to a second-line TKI. The first prognostic factor is the initial response to the first-line imatinib therapy. Jabbour et al. found that better survival rates were observed in patients who had experienced cytogenetic relapse or had been intolerant to imatinib therapy compared to patients who had hematologic relapse or resistance to imatinib [49]. Furthermore, patients who had experienced previous CyR to imatinib therapy had significantly better MCyR rates during second-line therapy. Patients with poor performance status and no previous CyR to imatinib therapy had a low probability of responding to second-generation TKI with poor EFS and could be offered additional treatment options [49].

Another predictive factor is early response to the second-line therapy. Tam et al. found that CyR to second-line dastinib or nilotinib at 3 and 6 months was strongly predictive of achievement of MCyR at 12 months [54]. In fact, 90% of patients showing no CyR at 3 to 6 months did not attain the target of MCyR at 12 months. A lower BCR-ABL1 transcript level at 3 months in patients taking second-line TKI was the most salient predictor of outcomes following second-line therapy [6].

Economic and patient burden of TKI failure: Relatively few studies have examined the economic and humanistic impact of TKI failure. This is somewhat surprising because resistance or intolerance to TKIs is expected to be associated with a substantial burden to both healthcare systems and patients, including costs and lower quality of life and mortality. Studies show that most of the related health care costs are associated with patient's non-adherence rates and side effects. As well, these patients have lower quality of life (QoL).

Healthcare costs associated with non-adherence: A retrospective analysis of medical claims data reported that the medication possession ratio (MPR) for imatinib patients was 77.7% and 31% of these patients experienced an interruption in their TKI therapy [43]. MPR is calculated as the number of days of medication supplied within the refill interval divided by the numbers of days in the refill interval as a proportion ranging between 0% and 100%, a lower MPR is associated with less adherence to therapy. The same study found that with every 10% decrease in MPR, there was a 14% increase in healthcare costs and a 15% difference in medical costs (excluding the cost of imatinib). Darkow et al. reported that patients with adherence below 50% experienced healthcare costs three times higher than patients with an MPR of 95% or higher [43]. In another retrospective claims database analysis, patients with low adherence to imatinib had significantly more all-cause inpatient visits and days than patients with high adherence to imatinib [35]. The low-adherence group experienced a 283% increase in healthcare costs compared to high-adherence patients.

Healthcare costs associated with side effects: Little published research has examined healthcare costs associated with TKI side effects and this work has focused on a few specific adverse events (AEs). Pleural effusion (PE) is a side effect that occurs very infrequently during imatinib treatment (0% to 2%) [55] and nilotinib treatment (1%) [56], but it is a relatively common side effect during dasatinib therapy (14% to 30%) [57]. In a retrospective study using claims data from 1999 through 2009, patients treated with TKIs who experienced PE had more inpatient days, hospitalization, outpatient visits, and emergency room visits than CML patients taking TKIs who did not experience PE [58]. The all-cause medical cost for PE patients ($88,526) was significantly greater than for PE-free patients ($30,434). PE patients also incurred higher CML-related medical costs compared to PE-free patients. Another cost-of-treatment analysis was based on resource utilization data for 48 patients with dasatinib-related PE at a large US cancer center. Sixty percent of PEs were managed medically, costing $750 per episode. Forty percent of PEs were more significant, with half of those requiring invasive procedures. The average cost of treating a PE was $2,062 to $2,700 for all severity levels and $6,400 to $9,000 for invasive procedures. This economic analysis using observed treatment patterns suggests that managing PE-adverse events in CML patients could be costly [59].

A small retrospective cohort study used patient records of 91 adults with CP CML who were treated at a university medical center in the Netherlands to estimate the cost of grade III/IV hematological AEs. Patients were included irrespective of the type of CML pharmacological treatment received. Overall, treatment costs per AE episode varied considerably, but the mean cost of an episode of anemia was €1,572, of thrombocytopenia €2,955, of neutropenia €1,152, and of febrile neutropenia €2,462 [60].

Quality of life: Many CML patients who receive TKI therapy remain in CP for years. Some patients experience few symptoms and an overall improvement in QoL after 6 months of imatinib treatment was reported in a study of tertiary care patients in Pakistan [61]. However, a significant number consistently experience moderate-to-severe levels of symptoms, including pain, fatigue, drowsiness, disturbed sleep, muscle soreness and cramping, and difficulty remembering. Many of these symptoms are probably treatment-related because they occur in patients with complete or major molecular remission [62]. The most severe symptoms (including edema, musculoskeletal pain, muscle cramps, and fatigue) identified in 25% to 30% of CML patients receiving imatinib remained consistently problematic over time and may occur with all TKIs [63]. The stability and chronicity of these symptoms is especially troubling from a patient-centric perspective, as even a mild symptom that persists for years can become problematic. Moderate-to-severe symptoms that are present for years can profoundly affect patients' functional status and QoL. This may lead patients to be non-compliant with therapy or abandon treatment entirely.

The QoL of individuals resistant to TKI treatment has rarely been examined. It is unclear whether aspects of QoL are unaffected by treatment or by becoming resistant or intolerant to first-line therapy. After first-line failure, CML patients' QoL suffers and is potentially improved with second-line therapy. One study reported that CP CML patients resistant or intolerant to imatinib had little impairment on most facets of QoL based on the Functional Assessment of Cancer Therapy - Leukemia (FACT-Leukemia) prior to beginning second-line treatment with bosutinib [64]. The FACT-Leukemia results observed at baseline were similar to the samples of individuals used to validate the measure. Specifically, patients' Physical Well-Being and Functional Well-Being subscales measuring lack of energy, presence of pain, ability to work, and ability to enjoy life showed little impairment. Patients also reported few symptoms of leukemia, despite being intolerant or resistant to imatinib treatment [64]. However, these data were collected within the context of a clinical trial; baseline QoL was assessed just prior to starting second-line treatment with bosutinib, rather than longitudinally during first-line TKI failure. An earlier clinical trial reported a trend of lower QoL scores in the imatinib arm among those who discontinued treatment [65].

Trask et al. examined QoL based on the FACT-Leukemia in CP CML patients prior to first, second, and third lines of TKI therapy from Phase II and III clinical trials as well as in advanced (both accelerated and blast phase) CML patients [66]. The results showed that QoL scores (across a variety of subscales and summary scores) worsened as the number of treatments increased and as the CML phase progressed, although these changes were not statistically significant across increasing numbers of treatments [66].

Suggestions for Future Research and Conclusions

Real-world research that examines resource utilization and healthcare costs associated with the use of first-, second-, and third-line TKI therapy and the associated failure will be useful in making treatment decisions. Descriptive treatment pattern studies that examine percentage of patients who switch TKIs from first and second line, as well as stop therapy altogether could clarify the actual rates of TKIs failure. It will also be valuable to identify and contrast indirect costs such as loss of productivity among patients during the period directly before they fail (i.e., switch) TKI therapy compared to a prior TKI period.

Only a few studies have examined costs of treatment for specific side effects associated with TKI therapy in CML patients. Additional analyses of a broader range of more serious side effects associated with TKI use, such as pulmonary arterial hypertension and vascular thrombosis [67], would help further identify the true cost of these

therapies. Although a fair amount of work has examined QoL and patient-reported outcomes, there is very little research specifically looking at QoL associated with TKI failure. Since TKIs can have significant side effects, it is likely that intolerance to TKIs may result in decreased QoL and an associated humanistic burden. The majority of work reviewed in this paper was conducted in the U.S. and E.U.; however, research that examines resistance and intolerance to TKIs and the subsequent burden of TKI failure in other countries or regions would provide a valuable addition to the literature.

TKIs have revolutionized the treatment of CML and have generally been found to be cost-effective as first-line therapy [68,69]. As long as CP-CML patients receive appropriate TKIs and adhere to treatment, they live close to normal lifespans [4]. However, not much is known about the burden of continuous TKI treatment. Over time, the patient's risk of TKI resistance or intolerance is likely to increase. Consequently, a greater understanding of antecedents and consequences of TKI failure is needed to make better treatment decisions. Of note, 2 new TKIs received FDA approval in 2012: ponatinib for adult patients with T315I-positive CML and bosutinib for adult patients with resistance or intolerance to prior CML therapy. Furthermore, omacetaxine, a protein translation inhibitor with a different mechanism of action than that of TKIs, also received FDA approval in 2012 for the treatment of CML with resistance or intolerance to two or more TKIs [70,71]. Future research is needed to determine the impact on healthcare costs and patients' QoL of switching to another therapy after first and second-line TKI failure, including these newer agents. TKI therapy alone does not cure the majority of patients with CML, additional therapeutic strategies should be considered to try to achieve a cure before intolerance and mutations occur.

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Authorship

Contribution: P.K., G.B., J.P.I., A.P, and B.T. were responsible for the evaluation and critique of previous research and all contributed equally to the writing of the paper. G.B. and A.P. were responsible for the conceptualization of the paper.

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