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REVIEW

Treatment selection after imatinib resistance in chronic myeloid leukemia

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Abstract Chronic myeloid leukemia (CML) is a progressive and often fatal malignancy of the blood. The harbinger of CML is a chromosomal translocation that results in the synthesis of the BCR-ABL fusion protein, a constitutively active tyrosine kinase. The advent of imatinib, an inhibitor targeted specifically for BCR-ABL, represented a significant medical advance in CML therapy. However, patients with CML can exhibit varying responses to first-line treatment with imatinib. While most patients respond to treatment, some may experience a loss of response or require treatment discontinuation due to toxicity. Frequent monitoring for resistance or intolerance is a requirement for recognition of suboptimal response. Mutational analysis of the patient's BCR-ABL alleles is also informative and may be predictive of a response to therapy. Published physician guidelines have highlighted these recommendations, but it is not clear if these guidelines are universally followed. One option in patients showing poor response to standard-dose imatinib of 400 mg is to escalate the dose. However, this option should be reserved for patients with minimal disease burden. Clinically available options mainly include second-generation tyrosine kinase inhibitors, such as dasatinib and nilotinib. Allogenic stem cell transplantations (for eligible patients) also should be considered. The disease and patient characteristics at the time of imatinib failure should be evaluated before choosing second-line therapy to optimize the therapeutic benefit without unnecessary delay.

Keywords Chronic myeloid leukemia · Dasatinib · Imatinib · Second-line therapy

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Introduction

Chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL) are hematopoietic stem cell disorders occurring in more than 60,000 individuals worldwide [1, 2]. Both CML and the less commonly diagnosed ALL constitute a patient population that presents a unique therapeutic challenge to oncologists/hematologists as the disease progresses. The disease progression occurs in three stages, initiating with a relatively slowly progressing chronic phase (CP), characterized by well-differentiated leukemic cells in the blood. This stage is typically indolent but is followed by an intermediate accelerated phase (AP), which is marked by poor control of white blood cell count and increased immature blasts observed in peripheral blood. AP persists for 3–9 months before a transition to blast crisis (BC) occurs, leading to metastasis, organ failure, and death. Patients in BC who do not receive treatment have a median survival of only 3–6 months [3, 4]. The transition from CP to the development of BC-CML can occur as rapidly as 3 years in those who have not sought medical intervention [5, 6].

A hallmark of CML, and a subpopulation of patients with ALL, is a genetic marker called the Philadelphia chromosome. This abnormality arises as a result of a rearrangement between genetic sequences from chromosomes 9 and 22. This transposition juxtaposes the Breakpoint Cluster Region (BCR) adjacent to the Ableson gene

and codes for the BCR-ABL fusion protein. BCR-ABL is a tyrosine kinase that continuously functions and results in constitutive signaling in a variety of intracellular circuits [7–9]. BCR-ABL expression has been shown to deregulate the cell growth, motility, angiogenic, and apoptotic mechanisms necessary for cellular transformation into a cancerous lesion. Some of the downstream signaling molecules activated by BCR-ABL include Ras/Raf/mitogen activated protein kinase (MAPK) [10–12], phosphatidylinositol 3 kinase (PI3K) [13–15], the STAT5/Janus kinase [16–18], and Myc [19–21]. In addition to BCR-ABL, these molecules also could serve as important targets for inhibition for drug development.

The transition from CP to advanced stages of CML is a poorly understood phenomenon. The pathogenesis of the disease may rely on the ability of BCR-ABL to deregulate genomic replication, resulting in the acquisition of additional genetic changes. These mutations also may arise in the BCR-ABL coding sequence itself, increasing mutagenic potential in a cell with an already unstable phenotype. The most common genetic mutations in patients in BC CML lie in p53, Rb, and INK41/arf genes [22–24]. These genes code for proteins critical in the maintenance of cellular homeostasis, and their modification has been repeatedly observed in a wide array of human cancers [25]. Therefore, directing inhibition of particular kinases and other signaling molecules in a specific and targeted manner has long been thought to represent an effective treatment strategy for CML.

The advent of tyrosine kinase inhibitors (TKIs) designed to inhibit BCR-ABL proved to be an improved therapeutic strategy in treating CML and Philadelphia chromosome positive (Ph+) ALL compared with interferon-alpha (IFNα). IFNα treatment had previously been well established and was once the therapy of choice in treatment of CML, despite the lack of durability in response (complete cytogenetic responses (CCyR) were maintained in just 8.5% of patients taking this therapy after 19 months) [26]. The first TKI approved for frontline CML and Ph+ ALL treatment was imatinib (Gleevec®; Novartis Pharmaceuticals, NJ, USA), which was designed to specifically bind to the catalytic region of the BCR-ABL enzyme. The phase III IRIS trial compared imatinib with IFNα in 1,106 patients and demonstrated superior response rates and survival with imatinib in patients with CP-CML [26]. Imatinib also was found to be tolerable in the study, with the highest grade adverse events (AEs) reported as cytopenias, elevated serum alanine or aspartate aminotransferase levels, pain, and nausea.

The recommended imatinib dosage varies depending on the phase of disease or leukemia type, and several different regimens are suggested: imatinib 400 mg/day is approved for patients who present with CML in the CP. Patients in AP- and BC-CML, as well as Ph+ ALL, are treated with an increased dosage of imatinib (600 mg/day) [1]. Although the toxicity profile of imatinib is tolerable and easily managed in the first line, there are a number of AEs that require monitoring during treatment. Additional AEs reported among patients taking imatinib include gastrointestinal symptoms, arthralgia/myalgia, rash, fatigue, and myelosuppression [27].

Not all patients will respond positively to treatment with imatinib and may have intrinsic resistance or develop resistance over time. The criteria for identifying resistance have been developed based on a lack of hematologic, cytogenetic, or molecular responses to therapy [1, 2]. Primary (or intrinsic) resistance is the lack of observable response when treatment commences and was observed in 24% of patients after 18 months of follow-up [26]. Primary resistance is defined as a lack of complete hematologic response (CHR) at 3 months, partial cytogenetic response (PCyR) at 12 months, and CCyR by 18 months [28]. Secondary (acquired) resistance is characterized by disease progression and a loss of therapeutic effect while on an imatinib regimen that had previously achieved a response. Secondary resistances were detected among 7% of patients examined in a 5-year follow-up study and relapsed disease was detected in approximately 17% after 5 years [29].

Another example of imatinib failure is intolerance, which is the discontinuation of treatment necessitated by drug toxicity. Intolerance to imatinib is a significant clinical issue, with 29% of patients requiring dose interruption, and 26% of these patients discontinuing therapy [30]. Intolerance is more frequently observed in patients in advanced stages of CML who have experienced a long duration of therapy [31–33].

Second-line TKI therapies now are available for those who fail the standard imatinib dose in the front line. Often, an escalated dosage of imatinib (600–800 mg/day) is prescribed for patients with CML or Ph+ ALL resistant to the standard dose [34]. However, this therapeutic option is not appropriate for patients who are intolerant. Although some resistance to imatinib has been resolved with dose escalation, this outcome is not consistent among all resistant patients [35–38]. Two other BCR-ABL TKIs currently are available in the event of imatinib failure. Dasatinib (Sprycel®; Bristol-Myers Squibb, NY, USA) has been shown to be 325-fold more potent that imatinib, and nilotinib (Tasigna®; Novartis Pharmaceuticals, NJ, USA) is an analog of imatinib.

This review evaluates these treatment options, provides guidance to clinicians for therapeutic selection, and describes agents currently in development. Resistance to imatinib has emerged as a significant hurdle to a positive therapeutic outcome for CML, and choosing second-line and third-line therapies is becoming a more prominent

concern to the health care practitioners. Furthermore, there is a need for new first-line therapies that may deliver superior response rates compared with imatinib in treatment-naïve patients or that may result in decreased levels of resistance to TKIs.

Imatinib failure and subsequent therapeutic options

Persistent Ph+ hematopoiesis, despite BCR-ABL inhibitor therapy, is the hallmark of resistance to TKIs. There are many postulated mechanisms of resistance, and a key one, structural modifications of BCR-ABL that interfere with drug binding, remains. These conformational changes are caused by point mutations in the BCR-ABL gene. More than 50% of resistant patients have acquired one or more point mutations in the Abl kinase domain. There are more than 40 different distinct kinase domain mutations linked to resistance to TKIs like imatinib. Many of these can be complementary to one another, and most of those found are in the catalytically important P-loop region of the enzyme. One of these mutations, a tyrosine to isoleucine substitution at position 315 (T315I), confers a resistance to all clinically available BCR-ABL inhibitors currently on the market and often is referred to as the "gatekeeper" mutation for CML.

Patients without point mutations may still be resistant to imatinib and other TKIs via a variety of mechanisms; amplification of the transcript level of the fusion protein is one such possibility. In this case, the standard dose of TKI may not successfully inhibit the overabundance of BCR-ABL produced [39]. Another possibility could be the overproduction of other tyrosine kinases, such as the Src-family kinase (SFK) member Lyn, whose expression can result in BCR-ABL–independent imatinib resistance [40]. In such an event, the Lyn kinase would continue to signal and deregulate intracellular growth pathways despite the adequate inhibition of BCR-ABL. Still another possible mechanism of resistance might be variations in the function and synthesis of the OCT-1 influx protein. The reduced expression OCT-1 has been correlated with insensitivity to imatinib in preclinical data [41]. Another suggested mechanism of resistance may be the ability of CML progenitor stem cells to toggle between resting and proliferating states as it circulates through the bloodstream. In such a case, the minimal BCR-ABL expression in the quiescent population would not be affected by TKI therapy [42]. These mechanisms of resistance, as well as imatinib intolerance, all suggest a switch to other second-line TKIs would be prudent in the effective management of CML and Ph+ ALL.

High-dose imatinib may be used as a method of acquiring response in the second-line if standard-dose imatinib proves insufficient [43]. A phase I dose-seeking trial of imatinib yielded a clear relationship between increasing imatinib dose and observed responses [44]. High-dose imatinib resulted in major cytogenetic response (MCyR) in 96% and a complete cytogenetic response (CCyR) of 90% in newly diagnosed patients with CP-CML [38, 45]. Of those who had failed IFNα, 96% achieved MCyR and 89% attained CCyR. However, this response may not be sustainable for long durations, and a propensity for AEs remains a significant treatment obstacle, particularly in patients with hematologic failure [38]. In other studies, the best attained cytogenetic responses on high-dose imatinib were soon lost by 43%–50% of patients [35, 37]. Furthermore, employing high-dose imatinib therapy in the second line is clearly inappropriate for those who are intolerant or exhibit resistances that render BCR-ABL insensitive to standard-dose imatinib.

Dasatinib is a newly approved, potent, multitargeted TKI. Targets of dasatinib extend beyond BCR-ABL to other proteins like SFKs, c-Kit, PDGFR-β, and ephrin A. Preclinical data suggest that SFK signaling contributes to proliferation and survival of myeloid cells expressing BCR-ABL [46]. Furthermore, many SFK members like Hck and Lyn are found in abundance in advance-stage CML patients [40, 47]. A feature unique to dasatinib is its ability to bind both the active and inactive conformations of BCR-ABL effectively. The therapeutic benefit of dasatinib in patients with all phases of CML and Ph+ ALL is well established in clinical trials. The *S*rc-ABL *T*yrosine Kinase Inhibition *A*ctivity *R*esearch *T*rials (START) program evaluated dasatinib for efficacy and safety in five large multicenter, open-label trials of patients with CML or Ph+ ALL and resistant or intolerant to imatinib [48–52]. This program demonstrated durable hematologic and cytogenetic responses across all constituent trials (Table 1). In total, 88% of patients with CML in the CP who achieved MCyR continued to respond after 24 months of follow-up [53]. Moreover, 91% of patients in the CP achieved complete hematologic remission, with most of these subjects eventually also achieving a CCyR [53].

The START-R trial evaluated patient response to dasatinib versus dose escalation of imatinib and found superior response rates among patients receiving dasatinib [51, 54]. CHR was achieved in more than 90% of patients on dasatinib (93% versus 82%; P=0.034), and CCyR also was improved versus high-dose imatinib (40% versus 16%; P=0.004). Furthermore, survival outcomes of patients taking dasatinib significantly increased after 21 months of follow-up [55]. There was a manageable and reversible safety profile of dasatinib recorded in the START program. The hematologic AEs consisted of commonly detected neutropenia and thrombocytopenia [1, 56]. The nonhematologic toxicities were reported as gastrointestinal AEs and fluid retention symptoms.

Table 1 Responses observed in a panel of phase II trials of dasatinib (START Program)[a] [48–52]

Study	CML phase or disease	Study size (n)	% CHR	% MCyR	% CCyR
START-C	Chronic	387	90	51	40
START-A	Accelerated	174	34	34	25
START-B	Myeloid/ lymphoid blast crisis	74/42	18/11	30/50	27/43
START-L	Ph+ ALL	48	29	44	38
START-R	Chronic	101	93	52	40

[a] All trials were single arm and open label except for START-R, which was a double-arm, randomized trial comparing dasatinib with high-dose imatinib. Responses reported in this table are for the dasatinib arm only

CCyR complete cytogenetic response, *CHR* complete hematological response, *CML* chronic myeloid leukemia, *MCyR* major cytogenetic response, *START* *S*rc-ABL *T*yrosine Kinase Inhibition *A*ctivity *R*esearch *T*rials, *Ph+ ALL* Philadelphia chromosome positive acute lymphocytic leukemia

The recommended dosage of dasatinib for patients with CP-CML is now 100 mg once daily. Initially, 70 mg twice daily was the approved dosage. This dosage was chosen based on a dose-escalation phase I trial that showed sustained inhibition of phospho-Crkl, a marker of BCR-ABL inhibition [57, 58]. An unexpected but manageable AE in the phase I trial was pleural effusion. In the phase II START program, where dasatinib 70 mg twice daily was the selected starting dosage, pleural effusion again occurred—more commonly in patients with advanced CML versus those in early CP.

In a longer-term follow-up of the phase I study, the data showed that once-daily dasatinib regimens had fewer incidences of pleural effusion reported. These results, combined with the fact that the mean delivered dose in the START-C trial was 101 mg, provided the rationale for a phase III dose-optimization trial [50, 51].

The phase III dose-optimization study was designed to evaluate the efficacy and safety of four different dasatinib doses in patients who had previously experienced imatinib failure [59]. This study showed that the 100-mg once-daily dosage was efficaciously equivalent to 70 mg twice daily but with an improved safety profile. Fewer patients experienced any grade of pleural effusion (7% versus 16%; P=0.024), grade 3/4 neutropenia (33% versus 42%; P=0.112), and grade 3/4 thrombocytopenia (22% versus 37%; P=0.004). This finding led to the approval of a 100-mg once-daily dosage of dasatinib for the treatment of CP-CML in patients either resistant or intolerant to imatinib. It is recommended that patients in AP-CML or BC-CML or patients with Ph+ ALL continue taking dasatinib 70 mg twice daily.

Another TKI that can be used in CML therapy after imatinib and dasatinib is nilotinib. This drug is an analog of imatinib with kinase targets that include BCR-ABL, PDGFR, and c-Kit receptors. Nilotinib has shown 10–50-fold greater potency than imatinib in inhibiting the unmutated form of BCR-ABL. The approval for a 400-mg twice-daily dosage of nilotinib was granted following a phase II study of patients with CML resistant or intolerant to imatinib [60]. Within this study, nearly half the study population achieved MCyR after 6 months, and this response endured for at least 18 months (Table 2) [36, 61–63]. Thirty-one percent of patients taking nilotinib obtained CCyR within 6 months of taking therapy. It should be noted that nilotinib must be taken before and after a 2-hour fasting period.

The safety profile for nilotinib indicates that myelosuppression, hepatotoxicity, and electrolyte imbalances are commonly reported adverse reactions [64]. Nilotinib also carries a black-box warning for prolonged QTc intervals and sudden death during therapy. These toxicities present challenges to patients with concomitant diseases, such as diabetes or endocrine dysfunctions, that may experience exacerbated symptoms while taking nilotinib.

Further therapies for treatment of CML

A number of new TKIs are in development and may reach the clinic within the next 2 years. Bosutinib or SKI-606 (Wyeth Pharmaceuticals, NJ, USA) is a dual BCR-ABL and SFK inhibitor currently in phase III trials. Bosutinib has shown 200-fold higher potency than imatinib for BCR-ABL and is active against a number of BCR-ABL mutants, but not T315I [65–68]. There is a manageable toxicity

Table 2 Response rates observed in nilotinib phase II trials [36, 62, 63]

Phase	Study size (n)	% CHR	% MCyR	% CCyR
Chronic	321	74	48	31
Accelerated	136	26	29	16
Lymphoid blast crisis	105	11	38	29
Ph+ ALL	31	13	48	32

CCyR complete cytogenetic response, *CHR* complete hematological response, *MCyR* major cytogenetic response, *NR* not reported, *Ph+ ALL* Philadelphia chromosome positive acute lymphocytic leukemia

profile associated with bosutinib that mainly consists of gastrointestinal AEs. Another TKI currently in early phase II studies is INNO-406. This agent also is a dual BCR-ABL/SFK inhibitor, with activity against PDGFR and c-Kit [69].

Combination approaches are being evaluated to assess the efficacy of TKIs with other agents. Decitabine (Dacogen®; MGI Pharma Corp., MN, USA) is a drug that has been shown to abrogate DNA methylation of tumor suppressor genes and has shown clinical activity in CML therapy [70, 71]. Decitabine, combined with the plant alkaloid omacetaxine (homoharringtonine), can complement imatinib therapy to achieve an antileukemic effect in cancer cells that demonstrate resistance to one or both drugs. Omacetaxine alone also has been shown to be an effective agent against T315I mutant BCR-ABL, achieving CHR in 47% and CCyR in 12% of patients with T315I who are in the CP [72]. A small trial of patients with imatinib resistance yielded hematologic and cytogenetic improvements in patients treated with decitabine, omacetaxine, and imatinib combination therapy [73].

Not all effective therapies for CML are kinase inhibitors. Allogenic hematopoietic stem cell transplantation (SCT) may be the only current treatment modality that aims for curative treatment of CML. Intriguingly, prior imatinib therapy is not exclusive to the efficacy of SCT, and indeed the two approaches may be favorably combined. SCT should be considered in patients who have experienced suboptimal or lost response to TKIs and are healthy, fit, and have a match-related donor available [74].

Clinician guidance to selecting treatment

Imatinib (400 mg/day) is the only clinically approved front-line TKI therapy for CML. Patients should be monitored for imatinib resistance based on National Comprehensive Cancer Network (NCCN) guidelines. The selection of second-line TKI therapy should be individualized to each patient, carefully considering drug efficacy and toxicity, as well as patient mutation data. In many cases, a patient's BCR-ABL genotype can serve as a prognostic factor to disease progression. For example, the response to dasatinib does not appear to be compromised among patients with F359C/V, which is a mutation in the catalytically important P-loop region of BCR-ABL [50]. However, patients with T315A/I, F317I/L, and V299L are unlikely to respond to dasatinib therapy. Nilotinib resistant mutations have been identified as T315I, Y253H, and E255V. It is noteworthy that both dasatinib and nilotinib are ineffective against T315I BCR-ABL. Indeed, this mutation is resistant to all available TKIs, and survival outcomes of patients with T315I remain stage dependent [75]. However, T315I and other nilotinib—or dasatinib-insensitive mutations are more likely to develop in patients with advanced CML versus those in early CP [76].

It is recommended that dasatinib therapy may be appropriate for patients with F359C/V mutations or base substitutions in the region coding for the P-loop. Nilotinib may be better suited for those patients with F317L mutations because this population achieved favorable response rates versus patients without F317L taking nilotinib [77]. Patients with T315I may find favorable outcomes by seeking alternative therapies than treatment with TKIs. As discussed, a dose escalation of imatinib in the second line is not an appropriate option for patients experiencing drug toxicity.

Pleural effusion also is a known AE for those receiving dasatinib, and this is especially true among patients in AP-CML or BC-CML. Other TKIs, like imatinib and nilotinib, also are not without risk of pleural effusion [27, 64]. Although, the incidence of pleural effusions is improved among patients with CP-CML receiving dasatinib with the advent of the 100-mg once-daily dose, nilotinib is the more appropriate therapy for patients with pre-existing lung conditions or high susceptibility to pleural effusion. Clinicians should be aware that a fasting requirement must be met for nilotinib administration. Both nilotinib and dasatinib have an impact on QT prolongation in preclinical studies. A novel agent, like bosutinib or INNO-406, may be considered ideal for patients at the highest risk of QT prolongation because these agents are not yet reported to cause cardiotoxicity. The same body of evidence does not exist for agents that are earlier in development. Finally, SCT remains a potential therapeutic modality provided the patient is young, fit, and a donor match can be quickly identified.

Conclusion

Imatinib is an established and effective front-line therapy that inhibits the BCR-ABL fusion protein. However, resistance and intolerance to imatinib remains a barrier to recovery for some patients. Healthcare practitioners should be aware of alternative second-line TKI therapies that are well tolerated and effective; dasatinib is a TKI that inhibits both BCR-ABL and SFKs. It is efficacious in treating CML with a manageable toxicity profile. Nilotinib also is clinically available and can be used to treat CML after failure of imatinib or dasatinib. Additional promising agents and therapies also are emerging in the effective management of CML. It is recommended that clinicians select treatment based on their patient's historical response, tolerance to AEs, risk factors, and development of potentially prognostic mutations.

Conflict of interest statement The authors of this manuscript have chosen not to provide information regarding any potential conflict of interest.

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