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Therapy Options in Imatinib Failures

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Key Words. CML • Imatinib intolerance • Imatinib resistance • Dasatinib • Nilotinib

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the mechanisms that result in resistance to imatinib in CML patients.
2. Employ the current guidelines that define resistance at various time points.
3. Assess the merits of the available therapeutic strategies following imatinib failure.

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ABSTRACT

Chronic myelogenous leukemia (CML) is defined by the presence of the constitutively active tyrosine kinase breakpoint cluster region/Abelson (Bcr-Abl), which activates numerous signal transduction pathways leading to uncontrolled cell proliferation. The development of the Bcr-Abl–targeted imatinib represents a paradigm shift in the treatment of CML, because treatment with imatinib resulted in significantly better patient outcome, response rates, and overall survival compared with previous standards. Despite this advance, not all patients benefit from imatinib because of resistance and intolerance.

Resistance to imatinib can develop from a number of mechanisms that can be defined as Bcr-Abl–dependent (e.g., most commonly resulting from point mutations in the Abl kinase domain) and Bcr-Abl–independent mechanisms (including the constitutive activation of downstream signaling molecules, e.g., Src family kinases), which could result in the activation of the pathway regardless of Bcr-Abl inhibition.

Clearly, new treatment approaches are required for patients resistant to or intolerant of imatinib, which can be dose escalated in patients who demonstrate resistance. This does not result in long-term responses. Hematopoietic stem cell transplantation is limited by the availability of matched donors and the potential for morbidity. Dasatinib, a dual Bcr-Abl/Src kinase inhibitor, has shown efficacy against all imatinib-resistant Bcr-Abl mutations except for T315I. A large trial program showed that dasatinib is effective in patients previously exposed to imatinib and has a manageable safety profile in all phases of CML and Philadelphia chromosome–positive acute lymphoblastic leukemia, resulting in its approval. Nilotinib, an analogue of imatinib, also has demonstrated activity in a similar patient population. These agents and less clinically advanced strategies are discussed in this review. *The Oncologist* 2008;13:424–434

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Table 1. Definitions of response

Response	Definition
Complete hematologic	WBC $<10 \times 10^9/l$ with normal differential; platelet count $<450 \times 10^9$; $\leq 1\%$ circulating immature cells (only if consisting of metamyelocytes); disappearance of all signs and symptoms of disease including palpable splenomegaly
Partial hematologic	WBC of $10\text{--}20 \times 10^9/l$; or normal WBC with $>1\%$ immature peripheral cells (blasts, promyelocytes, myelocytes, or metamyelocytes), or palpable splenomegaly, or the presence of other signs of disease
Cytogenetic	At least 20 marrow metaphases must be examined
Major	Ph+ metaphases, 0% (complete)
Minor	Ph+ metaphases, 1%–35% (partial)
Molecular	
Bcr-Abl undetectable	No detectable Bcr-Abl transcripts by nested RT-PCR or Bcr-Abl/Abl ratio $<0.001\%$
Major	Bcr-Abl/Abl ratio $<0.10\%$ or >3 -log reduction from baseline

Abbreviations: Bcr-Abl, breakpoint cluster region/Abelson; Ph+, Philadelphia chromosome-positive; RT-PCR, reverse transcriptase polymerase chain reaction.

INTRODUCTION

Chronic myelogenous leukemia (CML) is commonly defined by the presence of the Philadelphia chromosome, which arises from the reciprocal translocation of genetic material between chromosomes 9 and 22. The resultant Bcr-Abl oncoprotein, a constitutively active tyrosine kinase, activates numerous signal transduction pathways, leading to uncontrolled cell proliferation and reduced apoptosis [1].

The development of the Bcr-Abl–targeted imatinib represents a paradigm shift in the treatment of CML [2]. In a large, phase III trial, treatment with imatinib resulted in significantly better patient outcome, with higher response rates and a longer overall survival time compared with the previous standard treatment, interferon- α [3, 4]. However, despite the advance represented by imatinib, not all patients benefit from this treatment.

Primary, or intrinsic, resistance is defined by the National Comprehensive Cancer Network (NCCN) and LeukemiaNet guidelines as failure to achieve complete hematologic response (CHR) by 3 months, cytogenetic response (CyR) by 6 months, partial CyR by 12 months, and complete CyR (CCyR) by 18 months (responses defined in Table 1) [5]. After 12 months of treatment with imatinib, an estimated 16% of patients with newly diagnosed chronic phase (CP) CML in the phase III International Randomized Study of Interferon plus Ara-C versus STI571 in Chronic Myeloid Leukemia (IRIS) trial failed to achieve at least a partial CyR, and after 18 months approximately 24% failed to achieve a CCyR [3]. Importantly, in addition to those defined as having primary resistance, there is a subset of patients who respond suboptimally, that is, these patients may

still benefit from imatinib but are unlikely to have a favorable long-term outcome. For these patients, alternate therapies should be considered promptly to ensure progression does not occur before the introduction of a new therapy [6].

The incidence of secondary, or acquired, resistance (defined as the loss of response in patients who initially responded to treatment) also must be considered, with an estimated relapse rate of patients in this trial of 17%, with 7% of patients progressing to more advanced stages of disease [4]. Importantly, the incidence of resistance to imatinib is higher in patients with more advanced stages of CML, with relapse occurring in most patients who initially respond to treatment [4, 7, 8]. Additionally, imatinib intolerance also is recognized as a treatment concern, with 5% of patients discontinuing imatinib after 4.5 years of follow-up in the IRIS trial as a result of adverse events [9]. Despite the incidence of resistance, it should be noted that the relapse rate was significantly lower in patients who achieved a CCyR [10] and was even lower among patients who achieved a major molecular response (MMR) (≥ 3 log reduction in Bcr-Abl mRNA) [4, 11–13]. These two early indicators of efficacy are predictors of survival; indeed, the most recent version of the NCCN guidelines supports and emphasizes achieving CCyR as a key treatment goal.

MECHANISMS OF RESISTANCE

Bcr-Abl–Dependent Mechanisms

Resistance is often categorized as Bcr-Abl dependent or Bcr-Abl independent. Bcr-Abl–dependent mechanisms are thought to be the most common reason for the development of resistance, with the most common mechanism being

point mutations in the Abl kinase domain of the Bcr-Abl fusion protein. Indeed, more than 90 separate resistance-conferring point mutations at 57 residues in the Abl kinase have been documented [14], and these generally fall within four regions of the kinase domain: the ATP-binding loop (P-loop), the contact site (e.g., T315 and F317), the SH2 binding site (e.g., M351), and the A-loop [15].

The most frequently occurring mutations associated with Bcr-Abl are those of the P-loop [16] (30%–40% of mutations). Data show that patients who experience P-loop mutations have a poor prognosis for response and survival [16, 17]. P-loop mutations are more frequent in advanced CML, and accelerated or blast crisis phase CML is a significant factor in their development [18, 19]. Kinase assays have shown that P-loop mutations are 70- to 100-fold less sensitive to imatinib than native Bcr-Abl [20], and preclinical model systems have demonstrated that P-loop mutations have higher transforming activity than wild-type Bcr-Abl [21].

In contrast, some recent reports have suggested that P-loop mutations are not significantly associated with a worse prognosis compared with non-P-loop mutations [18, 22]. However, there is a confounding factor in the results of these more recent studies: the availability of second-generation tyrosine kinase inhibitors (TKIs), which were previously not available for patients following imatinib failure.

Another frequently occurring mutation, T315I, represents a key challenge in the treatment of CML. T315I is resistant to both imatinib [20] and the majority of the second-generation Bcr-Abl inhibitors, which are available in late-stage clinical trials. In addition to T315I, other mutations that are resistant to both imatinib and second-generation Bcr-Abl inhibitors have recently been identified [21]. New treatment strategies are currently in development to address this problem. Of note is that mutations associated with secondary imatinib resistance occur more frequently in later stages of the disease and are associated with older age, prior interferon therapy, initiation of imatinib in the accelerated phase or blast crisis, development of clonal evolution, high-risk Sokal score at diagnosis, and failure to achieve CCyR by 12 months [18, 19].

Additional mechanisms of Bcr-Abl–dependent imatinib resistance include increased production of Bcr-Abl. Gorre et al. [23] showed genomic amplification of *bcr-abl* in three of nine patients with imatinib-resistant CML, and Hochhaus et al. [24] demonstrated overexpression of Bcr-Abl mRNA in four of 37 imatinib-resistant patients. Although these studies provide evidence for increased Bcr-Abl protein translation, this mechanism has yet to be confirmed clinically.

Another mediator of imatinib resistance is the plasma protein α -1 acid glycoprotein (AGP), which acts to de-

crease intracellular concentrations of imatinib; AGP decreases imatinib concentration by binding imatinib at physiologic concentrations in vitro, resulting in reduced inhibition of Abl kinase in a dose-dependent manner [25]. Subsequent clinical studies have shown that plasma AGP binding is correlated with clinical responses to imatinib, although a causative role for AGP in human imatinib resistance has yet to be definitively established [26, 27]. Furthermore, imatinib is a substrate of a number of cellular efflux proteins, including P-glycoprotein (P-gp). In vitro studies have demonstrated that increased expression of P-gp results in imatinib resistance [28–30].

BCR-ABL–INDEPENDENT MECHANISMS

Although Bcr-Abl–dependent mechanisms are primarily responsible for the development of secondary, or acquired, resistance in CP CML, there are a number of Bcr-Abl–independent mechanisms that result in the development of resistance [29].

One such mechanism is the constitutive activation of downstream signaling molecules, which could result in the activation of the pathway regardless of Bcr-Abl inhibition, thereby resulting in imatinib resistance. The Src family kinases (SFKs) are likely to be an example of this Bcr-Abl signaling [32, 33]. SFKs have been demonstrated to regulate cell proliferation and survival, and have also been implicated in the development of late-stage CML, as well as Bcr-Abl–independent imatinib resistance [32–38]. Preclinical studies have shown that transfection of myeloid leukemia cells with kinase-defective Hck (an SFK) prevented the transforming activity of Bcr-Abl, and that the phosphorylation of the SH2–SH3 region of Bcr-Abl by SFKs is required for oncogenic activity and, therefore, CML pathogenesis [39].

Further studies have demonstrated that CML cell lines exhibiting imatinib resistance unrelated to Bcr-Abl overexpress Lyn and Hck. Furthermore, the coinhibition of SFKs and Bcr-Abl has been demonstrated to induce an enhanced apoptotic response [36, 40]. Clearly, there is a strong rationale for the use of dual inhibitors of SFKs and Bcr-Abl in the treatment of patients with imatinib-resistant CML.

Secondary clonal abnormalities have been shown to develop in approximately 5% of patients achieving a CCyR [41–43]. It has been hypothesized that alternative genetic aberrations synergize with Bcr-Abl in an evolution of resistance to therapy [44].

PRACTICAL RECOMMENDATIONS FOR RESPONSE ASSESSMENT

Monitoring patients to both evaluate the achievement of an early and deep response and ensure a continued, durable re-

Table 2. Time-based landmarks for evaluation of response

	3 Months	6 Months	12 Months	18 Months
Failure	No HR	>95% Ph+	>35% Ph+	>0% Ph+
Suboptimal	No CHR	35%–95% Ph+	1%–35% Ph+	0% Ph+; ≥3 log↓ in Bcr-Abl transcripts
Optimal	1–2 log↓ in Bcr-Abl transcripts	<35% Ph+	0% Ph+; ≥3 log↓ in Bcr-Abl transcripts	0% Ph+; ≥3 log↓ in Bcr-Abl transcripts

Abbreviations: Bcr-Abl, breakpoint cluster region/Abelson; CHR, complete hematologic response; HR, hematologic response; Ph+, Philadelphia chromosome-positive.

sponse is key in the treatment of CML. The most appropriate milestones for patients with CML are CCyR and MMR, which have both been established as important treatment parameters and independent prognostic factors for long-term survival [10, 45–47]. Indeed, numerous studies with imatinib have shown that both overall survival and progression-free survival times are longer in patients who achieve a CyR at 3 or 6 months [3, 12, 48–51]. Indeed, those patients who do not achieve these early treatment goals face a higher risk for disease progression and lower chance of achieving a CCyR or MMR later.

Clearly, there is an urgency in evaluating patients for signs of primary and secondary resistance. As a result, a number of time-based landmarks have been established to identify patients who are unlikely to respond to imatinib, and for those whose treatment is failing (Table 2) [5, 6, 52]. The current recommendations for monitoring response to imatinib treatment in CML are outlined in the recently updated NCCN guidelines [52]. In patients who are responding to treatment, cytogenetic testing should be performed after 6 and 12 months of therapy. If a CCyR has not been achieved at 12 months, a further cytogenetic evaluation should be performed at 18 months. Alternative therapeutic strategies should be implemented in those patients who have not achieved CHR at 3 months, and CCyR at 6, 12, and 18 months [52]. Even if a patient appears to be responding to therapy, particularly a CCyR, continued measurement of Bcr-Abl transcript levels in the peripheral blood by quantitative polymerase chain reaction is recommended every 3 months.

Screening for Abl kinase domain mutations is appropriate in patients with CP CML who experience inadequate initial response to imatinib therapy, and in those patients with any indication of a loss of response. The higher incidence of *bcr-abl* mutations observed in patients with advanced phase disease means that routine mutational screening should be performed in these patients every 3 months regardless of treatment response.

IMATINIB INTOLERANCE

Despite best supportive measures and dose modifications, imatinib intolerance is a significant clinical issue. In a recent data analysis of 216 patients by Hamdan et al. [53], 29% of patients required dose interruption, with a further 26% of these patients requiring discontinuation of treatment.

Adverse events that require treatment discontinuation include gastrointestinal symptoms, arthralgia/myalgia, rash, fatigue, and myelosuppression [54]. Patients unable to tolerate imatinib must be switched to an alternate therapy to prevent progression of leukemia [52].

APPROVED TREATMENT OPTIONS FOR PATIENTS WITH IMATINIB RESISTANCE OR INTOLERANCE

High-Dose Imatinib

Clearly, in patients who have experienced imatinib intolerance, escalating the dose of imatinib is not an appropriate strategy. Indeed, the strategy may not be feasible even in those patients who were able to tolerate standard-dose imatinib.

However, there is a rationale for this therapeutic approach in patients with imatinib resistance. Studies have shown that some *bcr-abl* mutations have less sensitivity to imatinib, but not complete resistance [55–57], and that Bcr-Abl amplification and overexpression can confer resistance. In these cases of resistance, it was hypothesized that greater doses of imatinib may be effective.

There are only limited clinical data published to support the use of high-dose imatinib in patients who previously demonstrated resistance to standard-dose imatinib. Dose escalation in a small series of imatinib-resistant patients to 600 or 800 mg/day induced CyRs in 19 of 34 patients with CP CML who experienced cytogenetic resistance or relapse when receiving 400-mg imatinib [58]. In another dose-escalation study, patients with imatinib resistance were dose escalated from 300 to 600 mg/day or from 400 to 800 mg/day. The efficacy results were modest, with 65% of 20 patients with previous hematologic resistance achieving a

Table 3. Summary of data from the START trials

Trial	Stage of disease	n of patients	Hematologic response (%)		Cytogenetic response (%)	
			Complete	Major	Complete	Major
START-C	Chronic CML	387	91	NA	49	59
START-A	Accelerated CML	174	43	63	28	37
START-B	Myeloid and/or lymphoid blast crisis	157	27	34	31	38
START-L	Ph+ ALL	46	NA	41	54	57
START-R	Chronic					
Dasatinib		101	93	NA	40	52
HD imatinib		49	82	NA	16	33

Abbreviations: CML, chronic myeloid leukemia; HD, high-dose; NA, not applicable; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; START, Src/Abl Tyrosine kinase inhibition Activity: Research Trials of dasatinib.

major hematologic response, and one patient experiencing a partial CyR. In 34 patients with cytogenetic resistance, 56% achieved a major CyR (MCyR) [58]. A further small study examined 16 patients with CP or accelerated phase (AP) CML who had relapsed or were refractory to imatinib. Efficacy results were again modest, with minimal CyRs (one partial and one minor) in patients with CP CML who were dose escalated from 400 to 600 mg/day, and five responses (two CCyRs, two partial CyRs, and one minor CyR) in patients with CP or AP CML after dose escalation to 800 mg/day [59]. When reviewing the data from all these studies, the MCyR rate is in the range of 35%–40% (with a CCyR rate of <20%). Allied with the disappointing response, the durability of response in these trials is limited (2–11 months), and patients with no prior CyR to imatinib do not appear to benefit from dose escalation. In addition, this strategy is not effective in disease harboring highly resistant *bcr-abl* mutations or Bcr-Abl-independent resistance.

Hematopoietic Stem Cell Transplantation

Allogeneic stem cell transplantation (SCT) is an established procedure that offers curative potential and could be considered as a second-line treatment choice. In patients <50 years of age and who receive a transplant <1 year after diagnosis, 5-year survival rates >70% have been attained [60, 61]. However, the application of this procedure is limited by the availability of matched donors and by the toxicity of the procedure in older patients [52]. Moreover, outcomes deteriorate with disease duration [61]. Further treatment options are therefore required.

The NCCN guidelines state that SCT is a treatment option for patients who received imatinib but who did not achieve a CHR within 3 months of treatment or a CCyR

within 12 months, or who have accelerated phase or blast crisis disease [52].

Dasatinib

Dasatinib is a potent, orally bioavailable, dual Bcr-Abl/Src kinase inhibitor, and is the first TKI approved in the U.S. and Europe for the treatment of imatinib-resistant and imatinib-intolerant patients across all phases of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Despite targeting Bcr-Abl, dasatinib is structurally unrelated to imatinib and binds multiple conformations of the Abl kinase domain [62–64]. In vitro, dasatinib demonstrated 325-fold greater activity against native Bcr-Abl compared with imatinib and has shown efficacy against all imatinib-resistant Bcr-Abl mutations with the exception of T315I [62, 63]. Dasatinib also is active against SFKs, c-Kit, platelet-derived growth factor receptor (PDGFR), and ephrin A receptor [65–68].

Phase I trials of dasatinib demonstrated preliminary evidence that dasatinib was effective, with a good duration of response and a manageable safety profile [69]. Further clinical evaluation was initiated with the Src/Abl Tyrosine kinase inhibition Activity: Research Trials of dasatinib (START) program, evaluating a dasatinib dose of 70 mg twice a day (b.i.d.).

Four of these studies (START-A, -B, -C, and -L) were large, multicenter, single-arm, open-label trials in imatinib-resistant or imatinib-intolerant patients with CP CML, AP CML, blast crisis (BC) CML, and Ph+ ALL [70–73], and the fifth (START-R) was a randomized study evaluating dasatinib 70 mg b.i.d. and high-dose imatinib in patients with previously documented imatinib resistance (Table 3) [73]. In general, the START program demonstrated durable hematologic responses and CyRs in patients for whom ima-

tinib therapy had previously failed for reasons of resistance or intolerance [70–73]. In START-C, which evaluated 288 imatinib-resistant and 99 imatinib-intolerant patients with CP CML, responses were achieved irrespective of the presence and location of *bcr-abl* mutations (with the exception of T315I, where no activity was observed). Of clinical importance is the fact that dasatinib had undiminished activity across subgroups, including in patients with P-loop mutations. The 15-month progression-free survival rate was 88% [70].

In patients with imatinib-resistant (161) or imatinib-intolerant (13) AP CML with a minimum of 9 months of follow-up, an impressive rate of MCyR (37%) was achieved [71]. The trend for an impressive response rate continued in patients with lymphoid ($n = 48$) or myeloid ($n = 109$) BC CML: MCyRs were achieved in 38% of patients [72].

START-R compared dasatinib (70 mg b.i.d.) with high-dose imatinib (800 mg/day) in CP CML that was resistant to imatinib at doses of 400–600 mg/day [73]. After a median follow-up extending to 21 months, MCyRs were achieved in 52% of patients receiving dasatinib and 33% ($p = .023$) of patients receiving imatinib, and CCyRs were achieved in 40% versus 16% ($p = .004$), respectively. In the small number of patients with P-loop mutations, MCyRs were only attained by those receiving dasatinib (50% versus 0%). Treatment with dasatinib resulted in a significantly longer progression-free survival time relative to high-dose imatinib ($p < .0001$) [73].

The START trials showed that dasatinib has a manageable tolerability profile: neutropenia and thrombocytopenia were common (with grade 3 and 4 events in CP disease occurring in 61% and 56% of patients, respectively), but were usually reversible and could be managed effectively by dose interruption or reduction. Nonhematologic toxicities consisted mainly of mild-to-moderate gastrointestinal symptoms (i.e., nausea and vomiting) and fluid retention. Grade 3 or 4 nonhematologic adverse events occurred in $\leq 5\%$ of patients. Pleural effusions occurred more commonly in advanced patients than in CP patients (17% versus 0%, respectively) and were managed with dose reductions and, when necessary, diuretic and/or steroid therapy. Importantly, there does not appear to be cross-intolerance between dasatinib and imatinib [70–73].

Another large trial recently evaluated the dosing of dasatinib in patients with CP CML. The 034 study compared 100-mg/day, 50-mg b.i.d., 140-mg/day, and 70-mg b.i.d. dasatinib, and demonstrated that, whereas all four regimens resulted in similar efficacy, the 100-mg/day regimen was associated with significantly lower incidences of pleural effusions (7% versus 16%) and grade 3 or 4 cytopenias (33%

versus 42%, and 22% versus 37%, for neutropenia and thrombocytopenia, respectively) than the 70-mg b.i.d. regimen ($p < 0.05$) [74]. The results of that study led to a recent change in the recommended daily dose for patients with CP CML from 70 mg twice daily to 100 mg once daily.

These results indicate that, in patients resistant or intolerant to imatinib, second generation TKIs such as dasatinib or nilotinib (see below) should be the preferred treatment options when SCT is not available or suitable.

Nilotinib

Nilotinib is an analogue of imatinib that was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CP or AP CML that is resistant to or intolerant of imatinib or other prior therapy [62, 75–77]. In vitro profiling showed that nilotinib is effective against all imatinib-resistant Abl kinase mutations except T315I, although a significantly lower activity (10- to 35-fold) has been noted against P-loop mutations compared with wild type [78, 79]. Recent data correlate this lower in vitro activity against P-loop mutations with clinical responses to nilotinib, showing that CCyRs do not occur in patients with P-loop mutations [80].

In a phase I dose-escalation study, nilotinib showed clinical activity in imatinib-resistant patients with all phases of CML or Ph+ ALL [80]. Among patients with CP CML, the CHR rate was 92% (11 of 12). In patients with AP and BC CML, hematologic responses were achieved in 72% (33 of 46) and 39% (13 of 33), respectively. The rates of MCyR were 35%, 27%, and 18% for patients with CP, AP, and BC CML, respectively.

The recent FDA approval of nilotinib was based on the safety and efficacy demonstrated in a single phase II open-label trial in patients with CP or AP CML. With a median treatment duration of 11.2 months, MCyRs were observed in over half of the patients with CP CML (179 of 320), with 32% experiencing CCyRs. The median duration of MCyR had not been reached at follow-up [81]. Nilotinib was also effective in patients with AP CML. With a median treatment duration of 6.9 months, MCyRs were observed in 31% of patients with AP CML, of which 19% were complete [82].

Trials of nilotinib are ongoing in patients with imatinib-resistant or imatinib-intolerant BC CML and Ph+ ALL. In patients with BC CML (median treatment duration, 2.8 months), CHRs were achieved in 24% (25 of 103) of patients with myeloid BC and 28% (eight of 29) of patients with lymphoid BC CML [83]. With a median treatment duration of 1.7 months, the CR rate in patients with imatinib-resistant or imatinib-intolerant Ph+ ALL was 24% (10 of 41) [84].

The most frequently reported grade 3 or 4 adverse events were thrombocytopenia, neutropenia, anemia, and biochemical abnormalities, including elevated serum lipase (15.3% in CP patients, 17.5% in AP patients, and 11.0% in BC patients) and hyperglycemia (12.2% in CP patients, 5.0% in AP patients, and 8.0% in BC patients) [85–87]. Biochemical abnormalities should be taken into consideration when treating a patient with concomitant diseases, such as diabetes or liver or kidney disease, and a history of pancreatitis. Nilotinib has been associated with prolongation of the QTc interval, and one patient in the phase I study had two nilotinib-associated adverse cardiac events, pericardial effusion (grade 1) and atrial fibrillation (grade 2) [80]. The safety profile of nilotinib has not yet been fully defined.

Based on the responses observed in these studies, nilotinib appears to have clinical activity in patients with CML and Ph+ ALL and should be considered as an alternative agent for those patients who are resistant to imatinib or intolerant to either imatinib or dasatinib. Similar to dasatinib, nilotinib should be considered as an alternative to allogeneic SCT in those CP CML patients who demonstrate resistance or intolerance to imatinib.

TREATMENT OPTIONS IN CLINICAL DEVELOPMENT

SKI-606 (Bosutinib)

SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, has a 200-fold greater potency for Bcr-Abl than imatinib and has demonstrated activity against a number of mutations, but not T315I [88]. Clinical studies of SKI-606 have demonstrated activity in CML and Ph+ ALL, but further investigation of this agent is required [89]. To date, results from the ongoing phase I/II trial indicate that SKI-606 has an acceptable toxicity profile [89]. In addition, these trials have demonstrated that approximately 30% of CP CML patients with imatinib intolerance or resistance achieved a CCyR within 3 months of initiating therapy.

INNO-406

INNO-406 is a 2-(phenylamino)pyrimidine Bcr-Abl inhibitor with anti-SFK activity, specifically Lyn, and like dasatinib, this agent also demonstrates activity against PDGFR and c-Kit [90]. Unfortunately, INNO-406 is not active against the T315I mutation. Preclinical studies have shown that INNO-406 is 25–55 times more potent than imatinib in Bcr-Abl–positive leukemia cell lines. Currently, a phase I trial of INNO-406 in CML and acute myeloid leukemia is under way.

MK-0457

MK-0457 (VX-680) is an Aurora kinase inhibitor with activity against Bcr-Abl. In preclinical kinase assays, this

agent was observed to inhibit autophosphorylation of the T315I Bcr-Abl mutant and demonstrated antiproliferative effects in CML cells derived from a patient harboring this mutation [91–93]. Because of the efficacy in patients with T315I mutation, which confers resistance to imatinib, dasatinib, and nilotinib, large clinical trials are eagerly awaited. Early clinical data from a phase I/II study demonstrated responses in all three patients with the T315I mutation [94]. The activity of MK-0457 against the T315I mutation may lead to its use as a combination partner with the approved and established imatinib and dasatinib. However, MK-0457 is currently only available as an i.v. formulation, which may limit its overall use. At least two other Aurora kinase inhibitors are currently under clinical development: PHA-739358 (phase II) and XL-228 (phase I).

FUTURE RESEARCH PERSPECTIVES

Other TKIs in development include the deacetylase inhibitor LBH589, which has demonstrated activity when combined with nilotinib against cultured or primary imatinib-resistant CML cells, including those with expression of Bcr-Abl T315I [95]. SGX70393 is a potent inhibitor of both wild-type Bcr-Abl (active and inactive conformations) and many clinically relevant imatinib-resistant Bcr-Abl mutants [96]. Additionally, histone deacetylase inhibitors have been shown to downregulate Bcr-Abl in CML cells, resulting in apoptosis, and combinations of these agents with either imatinib or heat shock protein 90 inhibitors have demonstrated enhanced antileukemic activity in vitro [97]. Agents such as WP1130, which is a second-generation tyrophenol derivative that has shown preclinical activity against both native and T315I-expressing leukemia cells [98], are also being developed, with antileukemic activity mediated through mechanisms other than tyrosine kinase inhibition. See Table 4 for a summary of targeted therapies that are either available or under development for the treatment of CML.

The role of TKIs in the preparation of patients for SCT, or as therapy after SCT, also requires further research. In a phase II study of patients with Ph+ ALL, imatinib was evaluated in combination with chemotherapy, and compared with historical controls, the combination provided a good quality complete remission and survival advantage [99]. Further investigation of TKIs before and after SCT should be undertaken.

Finally, the identification of specific mutations may have an important future role in dictating which therapy is attempted after patients develop secondary resistance to imatinib. For example T315I, E255V/K, and Y253H have been frequently seen in nilotinib-resistant patients, while in

Table 4. Molecular targets of available chronic myelogenous leukemia treatments and those currently being evaluated

Agent	Targets	Status
FDA approved		
Imatinib	Bcr-Abl, Kit, PDGFR-A, PDGFR-B	
Dasatinib	Bcr-Abl, Src family kinases, Kit, PDGFR-A, PDGFR-B	
Nilotinib	Bcr-Abl, PDGFR, c-Kit, EPHB4	
Investigational		
SKI-606 [100]	Bcr-Abl, Src	Phase I, II
INNO-406 [100]	Bcr-Abl, PDGFR, c-Kit, Lyn kinases	Phase I
MK-0457 [100]	Aurora kinase, Jak-2, Bcr-Abl	Phase I, II
LBH589 [100]	Histone deacetylase	Phase I, II, III
XL-228 [100]	Aurora kinase	Phase I
PHA-739358 [100]	Aurora kinase	Phase II
Preclinical		
SGX70393 [96]	Bcr-Abl	In vivo (mice)
WP1130 [98]	Jak kinases	In vivo (mice)
Abbreviations: Bcr-Abl, breakpoint cluster region/Abelson; Jak, Janus kinase; PDGFR; platelet-derived growth factor-receptor.		

dasatinib-resistant patients, T315I and F317L have been frequently observed.

CONCLUSION

The clinical availability of imatinib changed the natural history of CML, improving outcomes for patients. However, imatinib does not benefit everyone, and for many patients, imatinib resistance and intolerance render the treatment ineffective.

Intolerance to imatinib is immediately recognizable, and should be evaluated on an ongoing basis, but assessing the achievement and maintenance of response requires detailed evaluation. The early identification of patients with an inadequate response or resistance to imatinib therapy is crucial to enable timely intervention of therapy, which increases the patient's opportunity to experience the benefit of other agents. Detailed assessment of response at key intervention points is critical, as is the regular monitoring of response.

For those patients who experience imatinib failure to 400-mg imatinib because of resistance, there are two currently available treatment options: imatinib dose escalation and dasatinib. Although dose escalation with imatinib may have beneficial effects in some patients who experience imatinib resistance, the multiple mechanisms of resistance to imatinib highlight the requirement for alternate therapies. Furthermore, patients intolerant of standard-dose imatinib should not be dose escalated.

Dasatinib has demonstrated impressive efficacy and manageable tolerability (without cross-intolerance) in five large, multicenter, phase II clinical trials in patients with

imatinib-resistant or imatinib-intolerant CML across all phases and in Ph+ ALL. Furthermore, the results from START-R provide clinical evidence to support the rationale that a broader targeted, more potent agent, such as dasatinib, is more appropriate for the treatment of imatinib-resistant patients than high-dose imatinib. Likewise, similar responses have been seen with nilotinib for CP CML patients who develop secondary resistance to imatinib. Thus, nilotinib can be considered as an alternative therapy to allogeneic SCT for CP CML patients who are either resistant to imatinib or intolerant to imatinib or dasatinib.

The continued development of other second-generation TKIs, such as SKI-606, INNO-406, and MK-0457, provides further opportunities for physicians treating patients with CML. Furthermore, the opportunity of combining agents with established therapy, such as dasatinib or imatinib, or indeed with SCT, ensures ongoing evaluation of this therapeutic area.

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Therapy Options in Imatinib Failures

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