Targeting the BCR-ABL Signaling Pathway in Therapy-Resistant Philadelphia Chromosome-Positive Leukemia

Thomas O'Hare1,2, Michael W.N. Deininger3, Christopher A. Eide1,2, Tim Clackson4, and Brian J. Druker1,2

Abstract

Beginning with imatinib a decade ago, therapy based on targeted inhibition of the BCR-ABL kinase has greatly improved the prognosis for chronic myeloid leukemia (CML) patients. The recognition that some patients experience relapse due to resistance-conferring point mutations within BCR-ABL sparked the development of the second-generation ABL kinase inhibitors nilotinib and dasatinib. Collectively, these drugs target most resistant BCR-ABL mutants, with the exception of BCR-ABLT315I. A third wave of advances is now cresting in the form of ABL kinase inhibitors whose target profile encompasses BCR-ABLT315I. The leading third-generation clinical candidate for treatment-refractory CML, including patients with the T315I mutation, is ponatinib (AP24534), a pan-BCR-ABL inhibitor that has entered pivotal phase 2 testing. A second inhibitor with activity against the BCR-ABLT315I mutant, DCC-2036, is in phase 1 clinical evaluation. We provide an up-to-date synopsis of BCR-ABL signaling pathways, highlight new findings on mechanisms underlying BCR-ABL mutation acquisition and disease progression, discuss the use of nilotinib and dasatinib in a first-line capacity, and evaluate ponatinib, DCC-2036, and other ABL kinase inhibitors with activity against BCR-ABLT315I in the development pipeline.

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Background

Chronic myeloid leukemia and the BCR-ABL signaling pathway

Chronic myeloid leukemia (CML) is characterized by the (9;22)(q34;q11) translocation, which is cytogenetically visible as the Philadelphia chromosome (Ph) that gives rise to the BCR-ABL fusion protein (1, 2). BCR-ABL is a constitutively active tyrosine kinase that drives survival and proliferation through multiple downstream pathways (Fig. 1A; reviewed in refs. 3–5). CML typically begins with a chronic phase characterized by expansion of functionally normal myeloid cells; left untreated, the disease progresses to a fatal acute leukemia (blastic phase) of myeloid or lymphoid phenotype. The hallmark of blastic phase is loss of terminal differentiation capacity (6). A subset of patients with B-cell acute lymphoblastic leukemia (Ph+ ALL) also harbors the Philadelphia chromosome (7, 8). The indispensable role of BCR-ABL in CML was established with the use of a murine model in which recipients of BCR-ABL retrovirus-transduced bone marrow developed an aggressive CML-like myeloproliferative disorder (9). Mice expressing kinase-inactive BCR-ABL failed to develop leukemia, confirming a requirement for BCR-ABL kinase activity in leukemogenesis in vivo and suggesting BCR-ABL kinase as a therapeutic target (10).

The N-terminal coiled coil domain of BCR-ABL facilitates dimerization and trans-autophosphorylation (11, 12) (Fig. 1A). Autophosphorylation of tyrosine-177 of BCR-ABL promotes formation of a GRB2 complex with GAB2 and son-of-sevenless (SOS), triggering activation of RAS and recruitment of phosphatidylinositol 3-kinase (PI3K) and the tyrosine phosphatase SHP2 (13, 14). Signaling from RAS activates mitogen-activated protein kinase (MAPK) and enhances proliferation. PI3K activates the serine-threonine kinase AKT, which functions in: (1) promoting survival by suppressing the activity of forkhead O (FOXO) transcription factors (15); (2) enhancing cell proliferation by proteasomal degradation of p27 through upregulation of SKP2, the F-Box recognition protein of the SCFSKP2 E3 ubiquitin ligase (16); and (3) activation of mTOR, which leads to enhanced protein translation and cell proliferation (17, 18). An additional critical outlet of BCR-ABL is STAT5 activation through direct phosphorylation or indirectly through phosphorylation by HCK or JAK2 (19, 20); lack of STAT5 abrogates both myeloid and lymphoid leukemogenesis (21). Collectively, these
pathways modulate gene transcription (Fig. 1A). Additional signaling abnormalities characterize the transformation to blastic phase (6, 22).

**BCR-ABL inhibition in the treatment of CML**

The success of imatinib treatment for CML established that BCR-ABL is an excellent therapeutic target (23–26). Newly diagnosed chronic-phase patients with CML treated with imatinib exhibited 5-year rates of overall and progression-free survival of 93% and 89%, respectively (26). The cumulative failure rate was 17% at 60 months, peaking in year 2 at 7.5% and declining to <1% by year 5. During the 6th year of study treatment, there were no reports of disease progression (27). Imatinib therapy is much less effective in blastic-phase CML, and the more potent second-generation inhibitors dasatinib and nilotinib have not changed this. Thus, a more profound understanding of BCR-ABL signaling in blastic-phase CML is a prerequisite for developing better treatments. Three recent advances have revealed important new mechanistic details pertaining to disease progression in CML (28–31), as described below.

**BCR-ABL signaling and disease progression in CML**

The B-cell mutator activation-induced deaminase promotes disease progression and drug resistance in CML. Activation-induced deaminase (AID) is a B-cell–restricted antibody diversification enzyme that is involved in somatic hypermutation in mature, antigen-exposed B cells. AID is also present and active in a subset of patients with lymphoid blastic-phase CML or Ph+ ALL (28). The DNA
mutator activity of AID in this context is unchecked by protective mechanisms inherent in normal activated B cells, and is correlated with a dramatic increase in genetic instability. For example, copy number alterations and the introduction of point mutations bearing the AID fingerprint were detected in genes controlling cell cycle, DNA repair, and other critical cellular functions. Klemm and colleagues (28) established that abnormal expression of AID promotes disease progression through genomic instability and also plays a major role in generation of BCR-ABL point mutations, implicating AID in drug resistance. Because BCR-ABL kinase domain mutations are not limited to lymphoid disease, the authors investigated the possibility of lineage conversion and suggested that PAX5, a transcription factor that is important for B cell development and AID expression, may orchestrate interconversion of lymphoid and myeloid lineages. Alternatively, an as yet unknown mechanism could drive mutation acquisition in myeloid lineage cells.

miR-328 plays multiple roles in controlling myeloid differentiation in CML. The myeloid-specific transcription factor C/EBPα is a master regulator of target genes that are required for differentiation of CML progenitors into granulocytes. BCR-ABL influences C/EBPα levels by stabilizing heterogeneous nuclear ribonucleoprotein E2 (hnRNP E2), a posttranscriptional gene regulator that binds to the 5'-UTR of C/EPBα mRNA and blocks translation. In chronic-phase CML cells, C/EBPα expression is not substantially impaired by hnRNP E2, which is tightly regulated and kept at low levels. Conversely, C/EPBα is downregulated in blastic-phase CML through a BCR-ABL/MAPK/hnRNP E2 pathway (22), resulting in accumulation of blasts (32).

Eiring and colleagues (29) now reveal further complexity in the regulation of C/EPBα expression. Working from the observation that the microRNA miR-328 is subject to BCR-ABL–dependent downregulation in blastic-phase CML, they established multiple functions for miR-328 in a regulatory network that is central to the differentiation of myeloid progenitors. PIM1, a cell cycle and apoptosis regulator that is important for the survival of CML blasts, was identified as a direct target for canonical silencing by miR-328 in association with the RISC complex. More surprisingly, they found that miR-328 binds directly to hnRNP E2, acting as an RNA decoy that interferes with hnRNP E2-mediated repression of C/EPBα mRNA translation. The RNA decoy function is independent of proteins associated with the RISC gene silencing machinery. In total, restoration of miR-328 expression rescues differentiation by sequestering hnRNP E2, and impairs survival of leukemic blasts by interacting with the mRNA encoding the survival factor PIM1. C/EPBα further influences its own fate by binding to the miR-328 promoter and inducing its expression in myeloid progenitors. This study reveals a previously unrecognized function for microRNAs as RNA decoy molecules.

Musashi2-Numb signaling in CML disease progression. Recent studies disclosed that primary blast-phase cells express high levels of the RNA-binding protein Musashi2 in comparison with chronic-phase cells, whereas the Musashi2-repressed differentiation factor Numb shows the opposite expression profile (30, 31). Follow-on mechanistic studies in mouse model systems provided compelling evidence that loss or reduction in expression of Numb results in arrested differentiation and contributes to disease progression (30). NUP98-HOXA9, a chimeric transcription factor previously linked to blastic-phase CML, was shown to facilitate upregulation of Musashi2, leading to repression of Numb. Experimental attenuation of Musashi2 expression restored Numb expression and reinstated the chronic phase (30). Conversely, overexpression of Musashi2 in a mouse model led to increased cell cycle progression and, in cooperation with BCR-ABL, induction of an aggressive disease course (31). Given that it was detected in a majority of patients who went on to experience disease progression, Musashi2 upregulation also appears to be a reliable early indicator of poor prognosis (30, 31). Pharmacological manipulations that activate Numb and/or repress Musashi2 could open therapeutic avenues for preventing or controlling disease progression in CML and may also provide new approaches for the treatment of acute myeloid leukemia (31).

Mechanisms of resistance to ABL kinase inhibitors in CML
Imatinib is an effective first-line therapy for chronic-phase CML (33). However, some patients experience treatment failure after an initial response. Studies of relapsed patients revealed that BCR-ABL signaling is often reactivated at the time of resistance (34). Crystallographic analysis of the ABL kinase domain in complex with imatinib revealed that the drug binds exclusively to a catalytically inactive conformation of the ABL kinase (35, 36). Point mutations at residues that make direct contacts with imatinib or are critical for ABL to adopt an inactive conformation interfere with drug binding. Kinase domain mutations at >55 residues that confer varying levels of imatinib resistance have been identified (reviewed in ref. 37). These findings guided the design of the second-generation ABL inhibitors nilotinib, an imatinib derivative with ~30-fold higher potency (38), and dasatinib, a SRC/ABL inhibitor that is ~300-fold more potent than imatinib (39, 40). These inhibitors are effective against most BCR-ABL mutants, although the T315I “gatekeeper” mutation within the ATP-binding domain is completely resistant to all three approved therapies, exposing a critical gap in coverage (38). As a pan-BCR-ABL inhibitor, ponatinib (Table 1) is active against this mutant, and is in phase 2 clinical evaluation for refractory CML. Other new inhibitors, including DCC-2036 (41, 42) (Table 1), have also entered clinical testing for refractory CML.

Clinical-Translational Advances
New first-line therapies for chronic-phase CML
Imatinib remains the first-line CML therapy on the basis of its efficacy, side-effect profile, and safety record. Nonetheless, it is possible that another ABL inhibitor or combi-
nation of ABL inhibitors might represent a better first-line option for some or all patients. Possible benefits include: 1) reaching response milestones sooner, potentially resulting in a reduced risk of relapse (43); 2) being able to suppress a wider range of mutant clones, leading to a reduced risk of BCR-ABL mutation-based treatment failure; 3) improving side-effect and tolerability profiles; and 4) profoundly reducing and perhaps eradicating residual disease.

Recently, 14-month reports were issued from randomized phase 3 trials comparing either nilotinib (44) [300 or 400 mg twice daily; Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Philadelphia-Positive CML Patients (ENESTnd)] or dasatinib (45) [100 mg once daily; Dasatinib versus Imatinib Study in Treatment naïve CML Patients (DASISION)] with standard dose imatinib (400 mg once daily) as initial treatment. Both studies found the investigational treatment to be superior in terms of complete cytogenetic response (CCR) and major molecular response (MMR; defined as a BCR-ABL transcript level of ≤0.1% in peripheral blood on RQ-PCR as expressed on the International Scale) at 12 months, meeting the primary endpoints of the trials.

Table 1. Examples of New Targeted Agents with Potential Activity Against BCR-ABL{T315I} in Clinical and Preclinical Development

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Chemical Structure</th>
<th>Binding Site / Inhibitor Type</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ATP-binding site / ATP-competitive</td>
<td>Phase II</td>
</tr>
<tr>
<td>DCC-2036</td>
<td>(Currently Proprietary)</td>
<td>ABL switch control pocket / ATP-competitive</td>
<td>Phase I</td>
</tr>
<tr>
<td>GNF-2, GNF-5</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Myristate Pocket / Allosteric</td>
<td>Pre-Clinical</td>
</tr>
<tr>
<td>HG-7-85-01</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ATP-binding site / ATP-competitive</td>
<td>Pre-Clinical</td>
</tr>
</tbody>
</table>
These are important benchmarks because patients with newly diagnosed chronic-phase CML who achieve both CCR and MMR within the first 12 months of therapy have a low risk of long-term progression (26, 27, 46, 47). Of more importance from a clinical point of view, there was also early evidence of reduced progression to accelerated or blastic phase: 4% of patients treated with imatinib compared with <1% treated with nilotinib (ENESTnd), and 3.5% of patients treated with imatinib compared with 1.9% treated with dasatinib (DASISION). Although this evidence must be regarded as preliminary, the improved time to progression is arguably the most impressive result from these studies.

The availability of new and potentially more effective ABL kinase inhibitors ensures that imatinib will have competition as the first-line therapy for CML, and raises difficult questions about balancing costs against treatment with the “latest and greatest” medications. In fact, nilotinib was approved for first-line treatment of newly diagnosed, chronic-phase CML in June 2010, and dasatinib followed in short order in October 2010. The second-generation inhibitor bosutinib is also being tested in this setting (phase 3: NCT00574873; http://www.clinicaltrials.gov) (48, 49). Imatinib is an excellent therapy for the majority of patients with chronic-phase CML. Thus, it is impressive that potentially better options are positioned to take center stage within the first decade of the recognition that ABL kinase inhibitors could completely change the treatment of CML. The issue of whether administration of two or more ABL inhibitors as a cocktail or in a sequential rotation would equate with better disease control as compared with single-agent therapy for certain patients is certainly of interest, but it presents formidable difficulties in terms of clinical trial design.

Figure 2. Results from two independent clinical trials evaluating potential first-line use of nilotinib or dasatinib as compared with imatinib for newly diagnosed CML: A, ENESTnd; B, DASISION. Both studies demonstrated that the comparator drug was superior to imatinib with respect to the number of patients reaching a CCR and MMR at 12 months. Nilotinib and dasatinib were also superior to imatinib with respect to lowered incidence of progression to accelerated phase or blastic phase. Results from the two trials cannot be compared directly.
Targeting the BCR-ABL\textsuperscript{T315I} mutant: clinical candidates

Despite the approval of three therapeutic options, the cross-resistant BCR-ABL\textsuperscript{T315I} mutant and compound mutants selected on sequential ABL inhibitor therapy (50) present clinical challenges. In response to the need for a clinically useful BCR-ABL\textsuperscript{T315I} inhibitor, a variety of approaches are being pursued (51, 52).

**Ponatinib** (AP24534), a pan-BCR-ABL inhibitor. We recently reported the design and preclinical evaluation of ponatinib (Table 1), a potent inhibitor of native BCR-ABL, BCR-ABL\textsuperscript{T315I}, and other resistant mutants (IC\textsubscript{50}: 0.5–36 nM) (53–55). Ponatinib inhibited all tested BCR-ABL mutants in cellular and biochemical assays, suppressed BCR-ABL\textsuperscript{T315I}-driven tumor growth in mice, and completely abrogated resistance in cell-based mutagenesis screens, confirming its profile as a pan-BCR-ABL inhibitor. Interim data from a phase 1 trial in patients with refractory CML and hematologic malignancies have been reported (56). Pancreatitis was the dose-limiting toxicity at 60 mg daily, and 45 mg daily was selected as the recommended dose for further testing (phase 1: NCT00660920; http://www.clinicaltrials.gov). There was clear evidence of antileukemia activity, with major cytogenetic responses in 46% of chronic-phase patients resistant to second-line tyrosine kinase inhibitors, including 67% of those with the T315I mutation, as well as MMRs (56). A pivotal phase 2 trial of ponatinib is now under way (NCT01207440; http://www.clinicaltrials.gov). In a sense, ponatinib is positioned where nilotinib and dasatinib were a few years ago: under evaluation in the demanding setting of treatment failure. Farther on the horizon, if ponatinib can provide pan-BCR-ABL coverage and still exhibit a restricted kinase selectivity profile. It will be of interest to monitor the therapeutic potential of HG-7-85-01-type inhibitors.

**Allosteric inhibition by GNF-2.** The regulatory control mechanisms governing ABL kinase activity include an interaction between a myristoyl-modified glycine residue near the N-terminus and its cognate myristate-binding pocket (60, 61). Because the ABL N-terminal region is absent from BCR-ABL, the vestigial myristate pocket is unoccupied in the fusion protein. GNF-2 and the analog GNF-5 (Table 1) bind in the myristate-binding pocket, with surprising consequences. As a single agent, GNF-2 is a selective non-ATP competitive inhibitor of BCR-ABL activity (IC\textsubscript{50}: 138 nM for Ba/F3 BCR-ABL cells; 62) with a potency comparable to that of imatinib. Although neither GNF-2 nor GNF-5 is an inhibitor of BCR-ABL\textsuperscript{T315I}, a combination of high concentrations of GNF-5 and nilotinib showed inhibitory activity against this gatekeeper mutant in biochemical and cellular assays. One puzzling aspect of the cellular data (see Fig. 4A in Ref. 58) is the single-agent effectiveness of nilotinib against Ba/F3 BCR-ABL\textsuperscript{T315I} cells (IC\textsubscript{50} ~ 4 μM). We have not observed nilotinib to be a T315I inhibitor in cellular or biochemical assays (39, 53). The ability of an allosteric inhibitor to influence the conformation of the ABL kinase domain represents an exciting advance, and this process is being studied in more detail, particularly through the use of nuclear magnetic resonance spectroscopy (58, 63). The combination of GNF-5 with HG-7-85-01 exhibits cooperative inhibitory effects against the T315I mutant (59).

Preclinical BCR-ABL\textsuperscript{T315I} inhibitors: recent approaches

Whereas ponatinib and DCC-2036 have advanced to clinical evaluation, additional inhibitors are preclinical development. These include HG-7-85-01 (Table 1), which uses a modified nilotinib-dasatinib hybrid structure to avoid gatekeeper mutations (57), and GNF-2, an allosteric ABL inhibitor that has been shown to be effective in combination with ATP-competitive ABL inhibitors (Table 1) (58, 59).

**HG-7-85-01 combines elements of nilotinib and dasatinib to inhibit the T315I mutant.** An effort to design ATP-competitive inhibitors with activity against BCR-ABL\textsuperscript{T315I} and other clinically important gatekeeper mutants, such as c-KIT\textsuperscript{T670I} (gastrointestinal stromal tumors) and PDGFR\textsuperscript{αT674I} (hypereosinophilic syndrome), led to the discovery of HG-7-85-01 (Table 1). This compound incorporates design features of nilotinib and dasatinib but also has an unprecedented tolerance for a range of gatekeeper side chains. Despite this feature, however, HG-7-85-01 remains a relatively selective kinase inhibitor (IC\textsubscript{50}: 59 nM for Ba/F3 native BCR-ABL cells, and 140 nM for Ba/F3 BCR-ABL\textsuperscript{T315I} cells). HG-7-85-01 was less effective against Ba/F3 cells expressing several clinically important BCR-ABL mutants (IC\textsubscript{50}: 500–1000 nM for Ba/F3 BCR-ABL\textsuperscript{T315I} cells), but was effective when combined with nilotinib. HG-7-85-01 (57) is among the first kinase inhibitors that can target numerous gatekeeper mutant kinases and still exhibit a restricted kinase selectivity profile. It will be of interest to monitor the therapeutic potential of HG-7-85-01-type inhibitors.

**DCC-2036, an ABL switch control inhibitor.** DCC-2036 is an ABL inhibitor that accesses a distinctive switch control pocket that is transiently formed in the course of conformational regulation of the kinase (42). In Ba/F3 cellular proliferation assays, DCC-2036 was shown to be effective against cells expressing native BCR-ABL as well as several imatinib-resistant mutants (Y253F, T315I, and M351T) with IC\textsubscript{50} values of 45–74 nM (41). In a mouse bone marrow transplant/transplantation model of CML involving BCR-ABL\textsuperscript{T315I}, daily oral dosing of DCC-2036 resulted in significant prolongation of survival compared with vehicle-treated mice (42). DCC-2036 and related compounds are reported to be orally bioavailable, to exhibit a limited off-target profile, and to perform well in safety studies. DCC-2036 is undergoing phase 1 evaluation for use in imatinib-refractory CML (NCT00660920; http://www.clinicaltrials.gov), including patients with a T315I mutation.

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Future Developments and Considerations

There is reason for optimism in the realm of CML therapy. Nilotinib and dasatinib may reduce the rate of progression compared with imatinib, and for those patients who fail these inhibitors, third-generation drugs are in development that show activity against the T315I mutant, which has emerged as a common pathway of resistance. Thus, clinicians may soon have at their disposal a complete set of tools needed to curtail the emergence of BCR-ABL mutation-based resistance.

However, this is unlikely to be the end of tyrosine kinase inhibitor resistance in CML. BCR-ABL kinase domain mutations have attracted the most attention with respect to treatment failure, yet they are present in only 60% of patients with imatinib resistance. In the remainder of patients, poorly understood BCR-ABL–independent mechanisms of growth and survival are activated (Fig. 1B). In patients who are resistant to imatinib and have no detectable kinase domain mutation, kinase domain mutations are rarely detected if resistance to nilotinib also develops (70). Further, these patients respond poorly to third-line dasatinib (71). BCR-ABL–independent activation of LYN has been observed in some mutation-negative, imatinib-resistant patients who responded to dasatinib, consistent with dasatinib’s activity against both ABL and SRC family kinases (72–74).

We previously argued that BCR-ABL \(^{T315I}\)-driven escape from treatment with nilotinib or dasatinib suggests that the disease is still BCR-ABL–dependent (75). This appears to be consistent with emerging data from the ponatinib phase 1 study, wherein both cytogenetic and molecular responses were observed in patients with the T315I mutation who previously failed second-line therapy with nilotinib or dasatinib or both (56). Although establishing response rates for patients with the T315I mutation will be one focus of the ponatinib phase 2 trial, these preliminary findings suggest that the long-awaited goal of clinical containment of resistance due to single BCR-ABL kinase domain mutations may be soon be attained. Of note, T315I-inclusive compound kinase domain mutations (defined as two mutations in the same BCR-ABL molecule) can confer high-level resistance even to ponatinib, and remain an area of concern (53, 76). Although some mutations, most notably BCR-ABL \(^{T315I}\) and compound mutations, have proven difficult to address therapeutically with currently approved inhibitors, mutation-based relapses are better understood than those involving a partially BCR-ABL–independent resistance phenotype. Fortunately, the >10-year experience with ABL kinase inhibitors suggests that the proportion of newly diagnosed chronic-phase CML patients who have acquired BCR-ABL–independent clones is small, and that primary resistance may become a truly rare occurrence.

On the other hand, we do not expect advances in ABL inhibitor-based therapies as single agents to have a direct positive impact on disease eradication, given that the fount of disease appears to be largely insensitive to ABL kinase inhibitors (reviewed in ref. 77). More likely, approaches that create a situation of synthetic lethality or that target CML stem cells anatomically rather than biochemically will be required to translate profound responses into disease elimination. In the interim, clinical efforts should focus on keeping patients in the chronic phase and rapidly maximizing the depth of response.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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