



Loss of Response to Imatinib: Mechanisms and Management

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The treatment of chronic myeloid leukemia (CML) has been revolutionized by the small molecule BCR-ABL-selective kinase inhibitor imatinib. Although imatinib is highly effective initially and generally well-tolerated, relapse is increasingly encountered clinically. Until recently, for the majority of CML patients with disease no longer responsive to imatinib, as well as for patients with imatinib intolerance, few effective therapeutic options existed. Our understanding of the major mechanisms of imatinib resistance has led to the clinical development of two novel BCR-ABL inhibitors that harbor significant therapeutic promise in early clinical trial experience. These agents, dasatinib (BMS-354825) and AMN107, are more potent

inhibitors of BCR-ABL than imatinib, and moreover, harbor activity against nearly all imatinib-resistant BCR-ABL kinase domain mutant forms tested *in vitro*. Notably, neither of these compounds is effective against the imatinib-resistant BCR-ABL/T315I mutation. The potential availability of highly effective medications for the treatment of imatinib-resistant and intolerant cases of CML is expected to further complicate the timing of other effective therapies, such as allogeneic stem cell transplantation. Additionally, periodic genotyping of the BCR-ABL kinase domain to screen for drug-resistant mutations may play an increasingly important role in the future management of CML cases.

Although the majority of chronic phase patients with CML have durable hematologic and cytogenetic responses to imatinib, a subset of patients loses their best response despite continued treatment. Some of these patients progress to accelerated or blast phase CML, while for other patients, relapse consists of a loss of a previously established hematologic or major cytogenetic response. A minority of chronic phase patients with CML does not achieve a major cytogenetic response, and these patients are more likely to progress to blast phase.¹

Imatinib: Monitoring Response and Toxicity

For most CML patients, imatinib represents frontline therapy, and attainment of a complete cytogenetic response is a primary goal of treatment. The accepted standard method for assessing cytogenetic status remains bone marrow metaphase analysis; all patients should undergo periodic bone marrow biopsy. For chronic phase patients, the initial recommended dose of imatinib is 400 mg daily. It is generally accepted that 300 mg is the minimum dose necessary to achieve plasma concentrations sufficient to inhibit the kinase activity of BCR-ABL. Analysis of hematologic response to imatinib should be performed after 3 months of therapy. After 6 months of therapy, bone marrow evaluation including metaphase karyotype should be performed. Patients who fail to have any decrease in Philadelphia chromosome (Ph)-containing metaphases should be referred

for participation in a clinical trial with newer agents (see below) or treated with 600-800 mg imatinib daily as tolerated. Repeat marrow cytogenetic analysis should be performed 6 months after initiating therapy with 600-800 mg imatinib. Patients who fail to achieve a major cytogenetic response (less than or equal to 35% Ph-positive metaphases) should preferably be referred for participation in a clinical trial. For patients who achieve a complete cytogenetic remission, disease burden should be monitored with peripheral blood fluorescence *in situ* hybridization (FISH) or quantitative PCR (Q-PCR) every 3 to 6 months. A positive FISH test or a one log increase in Q-PCR should prompt a bone marrow examination with metaphase analysis. Additionally, all patients should undergo a yearly bone marrow analysis to assess for the Ph chromosome as well as clonal abnormalities in the non-Ph-harboring cells. Although dose escalation of imatinib based upon a significant increase in Q-PCR level is reasonable, due to the variability of most commercially available PCR assays, confirmation of an increased level should be considered. At this time, most clinical trials involving imatinib-resistant CML require a confirmed disease burden that is grossly detectable by bone marrow metaphase karyotype (> 35% Philadelphia chromosome-positive metaphases).

Although generally well-tolerated, imatinib is occasionally associated with significant toxicity. Hematologic toxicities are occasionally encountered, and imatinib therapy should be interrupted for any CTC grade 3-4 cytopenias. When cytopenias recover to no worse than grade 2, imatinib can be resumed at the same dose (if dose interruption is less than 2 weeks) or at a 25%-33% dose reduction (if dose interruption greater than 2 weeks). Doses lower than 300 mg should not be routinely employed. For neu-

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tropenia and anemia, growth factor support should be considered. Because cytopenias are commonly encountered in accelerated and blast phases, it is generally recommended to continue therapy despite cytopenias in these disease settings. Common non-hematologic toxicities include nausea associated with imatinib, which can be alleviated if the drug is taken with a large glass of water and a full meal. Muscle cramps can be minimized with tonic water and supplemental calcium. Grade 2 or greater liver function test abnormalities are an indication for dose interruption, with possible resumption of a reduced dose when abnormalities improve to Grade 1 or better.

Definition of Imatinib Resistance

Primary hematologic resistance, defined as failure to obtain a complete hematologic response despite therapeutic doses of imatinib (at least 300 mg daily), occurs in approximately 5% of cases. More commonly encountered (approximately 15% of chronic phase cases) is primary cytogenetic resistance, defined as failure to achieve either a major cytogenetic response (less than 35% Ph-positive marrow metaphases) after 6 months of therapy, or a complete cytogenetic response after 12 months of therapy. Secondary, or “acquired” hematologic and cytogenetic resistance refers to loss of a previously established response. After 42 months of follow-up, 16% of patients with “early” chronic phase (disease duration not greater than 6 months) developed secondary resistance or disease progression.² With 48 months of follow-up the incidence of secondary resistance or progressive disease in chronic phase cases previously treated with interferon- α was 26%; this rate was substantially higher in accelerated (73%) and blast phases (95%) of CML.

Mechanisms of Imatinib Resistance

While little is known about the molecular mechanisms responsible for the relatively rare cases of primary hematologic resistance to imatinib, the mechanisms of secondary resistance are largely understood.

BCR-ABL–dependent resistance

Initial studies of blast phase patients, whose responses to imatinib are nearly always transient, revealed that BCR-ABL activity is reactivated at the time of relapse in most cases.³ The significance of this finding is that despite the numerous secondary genetic alterations that are present in blast phase disease, disease relapse to imatinib most often is conferred by BCR-ABL, and attempts to once again inhibit BCR-ABL activity in these patients hold considerable therapeutic promise.

Kinase domain mutations in BCR-ABL represent the most common mechanism of acquired resistance to imatinib, occurring in 50%-90% of cases. To date, more than 40 different mutations have been associated with clinical resistance to imatinib.³⁻¹⁰ Imatinib has been shown to bind to the ABL kinase domain in the inactive, or closed, confor-

mation and to induce a variety of conformational changes to the protein upon binding.¹¹ While some resistance-associated mutations occur at amino acid positions implicated in directly contacting imatinib, the majority are felt to prevent the kinase domain from adopting the specific conformation to which imatinib binds.⁸ Studies have shown that some mutations confer only a moderate degree of resistance, and as a result, dose escalation is predicted to recapture responses in some cases.^{4,8,12}

Approximately 10% of resistant disease is associated with overproduction of BCR-ABL, typically through genomic amplification or the acquisition of additional Ph chromosomes.^{3,9,13-15} It is presumed that the intracellular concentrations of imatinib are insufficient to inhibit an increased level of BCR-ABL protein in these cells and again, increasing the dose of imatinib may be helpful.

BCR-ABL–independent resistance

Although most cases of acquired imatinib resistance are associated with reactivation of BCR-ABL activity through the mechanisms described above, there are clearly some cases of resistance that appear to occur through mechanisms independent of BCR-ABL (“primary resistance”).^{9,16} Approximately 30%-50% of blast phase patients do not achieve an objective response to imatinib, as compared with only 5% of chronic phase patients. Some of this discrepancy may be due to a higher likelihood of harboring an imatinib-resistant BCR-ABL kinase domain mutation in the blast phase as a result of a larger tumor burden. Indeed, a substantial fraction of cells were found to harbor imatinib-resistant mutations prior to imatinib therapy in 2 of 4 cases that failed to respond to imatinib,⁸ but this observation has not yet been shown to be operative in a comprehensive analysis of primary resistant cases. It is postulated that cell survival mechanisms that operate independently of BCR-ABL may be responsible for many cases of primary imatinib resistance, although our understanding of potential mechanisms of BCR-ABL-independent resistance remains limited. In some cases, reliance upon alternative pathways may be responsible for acquired resistance as well, as suggested by studies of primary cells in one case associated with a NUP98/DDX10 fusion gene in addition to the Philadelphia chromosome.¹⁶ Additionally, cell lines established from bone marrow samples obtained from imatinib-resistant patients have implicated SRC activation in some instances.¹⁷

Management of Imatinib Resistance

Due to the heterogeneity of resistance mechanisms to imatinib, it is unlikely that a single strategy to treat imatinib-resistant CML will be uniformly successful. As stated above, in patients with chronic phase disease, primary resistance is rare. As such, the majority of imatinib-resistant patients will harbor BCR-ABL kinase domain mutations. At the present time, the most promising strategy in cases of resistance involves efforts to overcome disease

driven by imatinib-resistant BCR-ABL kinase domain mutants and overexpression of BCR-ABL.

Dose Escalation of Imatinib

Preclinical studies have demonstrated that some imatinib-resistant kinase domain mutations confer only a modest degree of resistance to imatinib; therefore, dose escalation is predicted to be useful in a subset of cases. A substantial fraction of patients appear to respond to escalations of imatinib, although these responses are not typically durable.¹⁸⁻²⁰ It should be noted that many patients have significant difficulty tolerating higher doses of imatinib. It appears likely that the substantially increased potencies of newer ABL kinase inhibitors (see below) will render these drugs superior to the predicted twofold increase in exposure achieved with 800 mg imatinib. Clinical trials comparing these agents with 800 mg imatinib in this disease setting are ongoing.

Dasatinib (BMS-354825) and AMN107

Two investigational small molecule ABL kinase inhibitors, dasatinib (BMS-354825) and AMN107, have shown efficacy in phase I clinical trials for the treatment of imatinib-resistant CML and are being further evaluated clinically. The response data observed in phase I of both compounds were presented at the 2005 annual meeting of the American Society of Clinical Oncology.^{21,22} The long-term efficacy of these new inhibitors remains to be determined.

Dasatinib

Dasatinib is a thiazolecarboxamide that is structurally unrelated to imatinib. Co-crystal analysis has shown that the compound binds to the ABL kinase domain in the active (open) conformation¹⁶ and also inhibits SRC family kinases. Preclinical studies have revealed the compound to be approximately 300-fold more potent than imatinib^{23,24} and to harbor potent inhibitory activity against nearly all imatinib-resistant mutants tested.^{23,24}

The first cases to be treated with dasatinib in November 2003 were chronic phase patients with CML with hematologic resistance or intolerance to imatinib. Known imatinib-resistant BCR-ABL kinase domain mutants were detected in the majority of patients. Notably, the median duration of disease in this group of patients was 8 years. The observed complete hematologic response (CHR) rate in patients with resistance ($n = 31$) or intolerance ($n = 8$) to imatinib was 84% and 100%, respectively. At the time of analysis, the major and overall cytogenetic response rates were 35% and 52%, respectively, in imatinib-resistant patients, and 50% and 63%, respectively, in imatinib-intolerant patients. No dose-limiting toxicity was identified, and phase II studies have completed accrual.

The phase I study was later amended to allow enrollment of imatinib-resistant and -intolerant patients with accelerated and blast phase CML, as well as Ph-positive acute

lymphoblastic leukemia (ALL). In 10 patients with accelerated phase, with a median disease duration of 6 years, the CHR rate was 50%. The overall and complete cytogenetic response rate was 40% and 30%, respectively. The aggregate experience with 34 patients with blast phase/Ph-positive ALL, with a median disease duration of 3 years, revealed a CHR rate of 28%, with overall and complete cytogenetic responses noted in 56% and 19%, respectively. Grade 3-4 hematologic toxicity occurred in the majority of these patients, and the most common grade 3-4 non-hematologic toxicity was pleural effusion.

The BCR-ABL kinase domain of all patients was sequenced prior to initiation of dasatinib. Cases harboring the T315I mutation, which is highly resistant to dasatinib in preclinical studies,^{23,24} prior to dasatinib therapy were not associated with objective responses. In 4 of 5 cases of blast phase CML/Ph-positive ALL who developed acquired resistance to dasatinib, the T315I mutation was detected at the time of relapse.²⁵

AMN107

AMN107 is an aminopyrimidine that is a structural derivative of imatinib. Like imatinib, AMN107 binds the ABL kinase domain in the inactive conformation, but with approximately 25-fold increased potency relative to imatinib. Importantly, this compound harbors activity against most imatinib-resistant mutations tested.²⁶ Unlike dasatinib, AMN107 does not inhibit SRC family kinases.

A phase I trial of AMN107 initially enrolled patients with imatinib-resistant accelerated and blast phases of CML, as well as Ph-positive ALL.^{27, 28} In imatinib-resistant accelerated phase disease, the CHR rate in 50 patients was 51%, with overall and complete cytogenetic response rates of 38% and 14%, respectively. In 24 patients with myeloid blast phase, CHR was observed in 17%. Overall and complete cytogenetic responses occurred in 25% and 8% of patients, respectively. Of 9 patients with lymphoid blast phase CML, CHR was achieved in 11%, with overall and complete cytogenetic responses in 22%. Among 10 patients with Ph-positive ALL, 10% achieved CHR, and no cytogenetic responses were observed. Grade 3-4 hematologic toxicity was observed. The most common grade 3-4 non-hematologic toxicity consisted of rash and hyperbilirubinemia.

The study was later amended to include imatinib-resistant chronic phase CML patients. Analysis of 15 patients revealed achievement of CHR in 80%, with overall and complete cytogenetic response rates of 40% and 13%, respectively.²⁷

The majority of patients with known kinase domain mutations responded. No response was observed in a patient with the T315I mutation.

Allogeneic Stem Cell Transplantation

Although molecular therapy for CML is highly effective and generally non-toxic, it is unclear whether long-term outcomes with imatinib and other therapies will be equivalent to cases treated with allogeneic stem cell transplantation (allo-SCT), which is associated with the highest percentage of long-term disease-free survival of any therapy. It should be noted that a small number of interferon-treated patients have enjoyed disease-free survival for greater than 10 years, despite cessation of therapy. Since imatinib became available, allo-SCT for CML is becoming increasingly infrequent. Clearly, younger patients with chronic phase disease and suitable donors should be informed about the risks and benefits of transplantation. The high survival rate (94%) of early chronic phase patients 42 months after initiating imatinib therapy suggests that it may be several years before the survival curves of allo-SCT- and imatinib-treated patients intersect.² Most experts therefore believe that a trial of imatinib therapy is reasonable in nearly all cases of CML. Dasatinib and AMN107 will likely further delay the timing of allo-SCT in many cases. Clearly, the few patients with BCR-ABL-independent mechanisms of imatinib resistance will most likely not obtain any benefit from kinase inhibitors, and these patients should proceed to allo-SCT if possible.

Given the poor long-term success of imatinib for the treatment of accelerated and blast phase CML, as well as Ph-associated acute lymphoblastic leukemia, it is unlikely that currently available kinase inhibitors will result in long-term disease-free survival in the majority of cases. For imatinib-resistant patients with these disease phases, a trial of dasatinib or AMN107 is reasonable. Given the lack of effective long-term therapies for accelerated and blast phase CML, patients achieving a morphologic bone marrow remission who are eligible for allo-SCT should be considered for consolidative transplant.

Other Approaches and Agents

Nearly all patients treated with imatinib harbor detectable minimal residual disease and can therefore be considered to have "primary molecular resistance." Approaches involving immunotherapy to reduce or eradicate minimal residual disease burden are under investigation. Several molecules that can synergize with imatinib in vitro, such as inhibitors of RAF, farnesyl transferase,²⁹ mTOR,^{30,31} and cyclin-dependent kinases,³² are undergoing evaluation in clinical trials.

Future Directions

By minimizing susceptibility to drug-resistant kinase domain point mutations in preclinical studies, dasatinib and AMN107 represent important advances in CML targeted therapy.^{23,24,26} The early successes of these compounds suggest that the majority of patients with imatinib-resistant chronic phase disease will achieve objective responses, but the durability of responses with these agents remains to be

defined. Clearly, the BCR-ABL/T315I mutation represents an important gap in the coverage of both compounds, and it is possible that the majority of acquired resistance to these compounds will be mediated by selective outgrowth of cells harboring this mutation. Strategies to override resistance mediated by the T315I mutation represent the next major frontier in the targeted treatment of CML and, coupled with existing ABL kinase inhibitors, may help improve survival in accelerated and blast phase cases. A recently described compound inhibits the growth of BCR-ABL-expressing cells in a non-ATP-competitive fashion.³³ This compound harbors potent activity in the low nanomolar range, irrespective of the identity of the BCR-ABL kinase domain mutation, including T315I. Searches for a selective inhibitor of BCR-ABL/T315I are ongoing. For the relatively uncommon patients with mechanisms of imatinib resistance that are independent of BCR-ABL and other kinases inhibited by dasatinib and AMN107, transplant should be pursued where possible. Clinical trials involving agents with activity in CML that act through BCR-ABL-non-specific mechanisms represent another viable option. A more individualized approach to therapy may be possible once a more complete understanding molecular pathways involved in these cases is established.

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