Strategies for Overcoming Imatinib Mesylate Resistance in Chronic Myelogenous Leukemia

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Imatinib mesylate was approved for the treatment of chronic myelogenous leukemia more than 5 years ago. This drug enabled us to put a very high percentage of patients into hematologic, cytogenetic, and molecular remission. Some patients were resistant to Imatinib from the onset of the treatment whereas others became resistant after showing an initial response to Imatinib mesylate. Various strategies have been tried to overcome the resistance to this drug including using newer combinations, higher dosage of Imatinib and development of newer compounds. This article will discuss these strategies in detail.

Keywords: chronic myelogenous leukemia, imatinib mesylate, resistance

INTRODUCTION

Most of the patients suffering from chronic myelogenous leukemia (CML) achieve a durable response with Imatinib therapy, but a small percentage of patients are resistant to the beneficial effects of this drug. Some patients do not respond to Imatinib from the onset of the treatment whereas others lose their response to the therapy and progress to accelerated or the blast phase of the disease. Patients who do not achieve a major cytogenetic response to Imatinib therapy is more likely to progress to the blast phase.

DEFINITION OF RESISTANCE TO IMATINIB AND ITS INCIDENCE

Resistance to Imatinib maybe primary or secondary. Primary resistance is lack of efficacy from the onset of treatment with Imatinib whereas secondary resistance develops after an initial response to Imatinib.

Resistance maybe further divided into hematologic, cytogenetic, or molecular. Hematologic resistance is defined as lack of or loss of normalization of blood counts or spleen size in patients in chronic phase of CML. In advanced disease, hematologic resistance is defined as lack of return to chronic phase of CML. Cytogenetic response is defined according to percentage of Ph+ cells in bone marrow. Major cytogenetic response is <35% Ph+ metaphases whereas complete cytogenetic response is total absence of Ph+ metaphases. More than 90% of cytogenetic responses are apparent within 6 months of initiation of Imatinib therapy. Major molecular response is defined as >3 log reduction of BCR-ABL transcripts or BCR-ABL/ABL ratio of <0.1. In patients treated with Imatinib, primary cytogenetic resistance is 3 times more likely as compared with primary hematological resistance (15% vs. 5%).

Data after more than 48 months of initiating therapy with Imatinib, has shown that in patients previously treated with Interferon, 82% patients were still alive and 80% were free from progression to accelerated or blast phase of CML. As the duration of chronic phase averaged about 3 years before the introduction of Imatinib, hence Imatinib improves survival in such patients. Approximately 60% of these patients continued to be on Imatinib therapy. Results were better in the patients who achieved a Partial cytogenetic response by 3 months with more than 94% of these patients being alive. Response rates to Imatinib were worse in patients in the accelerated phase with 73% patients showing disease progression despite being treated with the recommended dosage of 600 mg/d.
Less than 10% of the patients in Blast crisis were alive and even among these patients many had undergone allogeneic transplantation.

The percentage of patients with mutations is the lowest in the early phases of chronic phase. It increases in the later phases of chronic phase and with disease progression.

**MECHANISM OF RESISTANCE TO IMATINIB**

Mechanism of primary resistance to Imatinib is not well understood but mechanism of secondary resistance is much better understood.

**BCR-ABL–dependent resistance**

Point mutations within the Abl kinase domain in the BCR-ABL gene are associated with clinical resistance to Imatinib in CML. The presence of missense mutations was subsequently found to be associated with a greater likelihood of subsequent progression to accelerated phase and blast crisis. Hence, irrespective of hematological response in the first few months of treatment, monitoring for emerging mutations during this period may detect patients with a worse prognosis.

Kinase domain mutations of BCR-ABL are the most common mechanism of acquired resistance to Imatinib. Here Imatinib binds to ABL kinase domain in the active conformation leading to conformational changes at the binding site. Some mutations confer only moderate resistances, which maybe overcome by increasing the dosage of Imatinib.

Rarely overproduction of BCR-ABL through gene amplification can lead to acquired resistance, which again may be overcome by increasing the dosage of Imatinib.

Mutations with in the P loop had the worst prognosis. In one study, 12/13 patients (89%) died as compared with 21% patients who died when they had a non-P loop mutation over a similar time period.6

**BCR-ABL–independent resistance**

This is the main mechanism for primary resistance. SRC activation may be the mechanism of such resistance in some patients.7

**OVERCOMING IMATINIB RESISTANCE**

Because mechanisms of resistance to Imatinib vary, different strategies have to be used to overcome the resistance.

**Increasing initial dosage**

Response to Imatinib is much higher, if the drug is started at an early stage of the chronic phase as compared with initiating therapy at an advanced stage of the chronic phase. Various dosages from 400 to 800 mg per day have been explored as the initial dosage. Patients who received 800 mg/d achieved complete cytogenetic response in more than 90% of the patients and none of these patients progressed to the more advanced stages of the disease.6 Hence, dose escalation maybe a strategy to avoid resistance probably by minimizing the opportunity for genetic instability, which can lead to resistance.

**Dose escalation**

Patients who were resistant to Imatinib were exposed to 600 to 800 mg of Imatinib daily. Sixty-five percent of these patients achieved a complete hematological response and 56% showed complete cytogenetic response. Similarly, patients in Blast crisis, higher responses were seen in patients whose dosage was escalated. The higher rate of response was thought to be due to the underlying reason for resistance, which was thought to be ABL kinase domain mutations. Another reason why such a strategy may succeed is that multidrug resistance may be the cause of resistance to Imatinib and this may limit the intracellular concentration to Imatinib. Hence increasing the intracellular concentration by increasing the daily dosage may help such patients.

**Interruption of imatinib therapy**

Rationale of this approach is thought to be effective when the Imatinib-resistant clone severely impairs drug binding as seen in BCR-ABL point mutations. This approach relies on the reappearance of the nonmutant BCR-ABL clones to suppress the mutant clone by removing its competitive advantage.

**Combination therapy**

Upfront combinations have been tried in several clinical trials including combination of Imatinib and Interferon.9 One novel approach is to stimulate the host immune response by vaccinating patients with a BCR-ABL fusion peptide.10 Addition of drugs like Lonafarnib, Ara-C, and LY294002 to Imatinib results in enhancing the susceptibility of these cells to therapy.11 Addition of Rapamycin may help overcome moderate resistance to Imatinib.12 Several populations of primitive quiescent BCR-ABL positive cells are inherently resistant to Imatinib therapy. Eradication of these populations of resistant cells may help in achieving a cure for CML.
Newer drugs

Dasatinib (BMS 354825)

This is an inhibitor of both SRC and ABL kinases and is 300-fold more potent than Imatinib. This drug is well tolerated and has a half-life of 4 to 5 hours and the maximum tolerated dose has not been reached in phase 1 clinical trials. Considering the short life, the drugs will need to be dosed twice a day. Most of the mutations in the BCR-ABL domain can be overcome with this compound except mutations in the 315T domain. In the phase 1 study 31 patients who were either resistant or intolerant to Imatinib, hematologic responses were seen in 80% patients with cytogenetic responses being seen in 45% patients. This drug is also being investigated in the treatment of prostate cancer due to its effects on SFK and focal adhesion kinase signaling.

AMN-107

This is a novel orally bioavailable aminopyrimidine which is an ATP-competitive inhibitor of BCR-ABL. This drug was found to be 43 to 60 times as potent as Imatinib in laboratory studies. In Imatinib-resistant patients, AMN 107 achieved complete hematologic responses in 51% patients. Complete cytogenetic responses were seen in 14%. Similarly encouraging results were seen in patients in both lymphoid and myeloid blast crisis. No responses were not seen in any patients with T315I mutation.

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This drug is a non-ATP competitive inhibitor of BCR-ABL. It inhibits CML cells at concentrations below 10 Nm. More importantly, this drug induced apoptosis in all known Imatinib-resistant mutations in concentrations below 10 Nm. This drug is also a powerful inhibitor of LYN kinase which has recently been shown to another mechanism of Imatinib resistance. This drug probably will have the potential of being used alone or in combination with other agents.

Miscellaneous agents

Newer agents like heat-shock protein (17-AAG) and mTor inhibitors (RAD003) are also being investigated.

Role of allogeneic transplantation

Despite advances made in the pharmacotherapy as mentioned earlier, allogeneic stem cell transplantation still remains an important treatment. This is the therapy, which provides the highest disease-free survival as compared with the various pharmacotherapies. This is especially important in the younger patients who should be explained the pros and cons of various treatments. In patients who do not achieve the expected response in the first few months, allogeneic transplant is a very attractive option.

REFERENCES


