Second-Line Therapy for Patients With Chronic Myeloid Leukemia Resistant to First-Line Imatinib

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Abstract

The treatment of chronic myeloid leukemia (CML) with *BCR-ABL1* tyrosine kinase inhibitors (TKIs) is highly effective in reducing disease burden and prolonging overall survival in the majority of patients. Up to one-third of patients who initiate first-line TKI therapy with imatinib, however, experience resistance to treatment, presenting as a lack or loss of response or as disease progression. Sokal or Hasford risk score at baseline and achievement of early molecular response to treatment may help identify patients at risk for resistance to first-line TKI therapy and poor prognosis. Approximately half of the patients with resistance to TKI treatment have mutations in the *BCR-ABL1* kinase domain. Mutation status can be informative and should be considered alongside other factors, including patient history and drug safety profile, in second-line treatment choice. Factors present at the time of initiation of second-line TKI therapy, such as response to initial therapy, as well as achievement of molecular response within the first 6 months of second-line TKI therapy, have value in predicting response and survival outcomes. Given the expanding number of therapeutic options currently approved (FDA), an understanding of the clinical data supporting each of the options for second-line treatment would enable clinicians to develop treatment plans based on the best evidence-based information. This review estimates the incidence rate of TKI resistance that might be expected in the first-line setting, outlines practical approaches to determine TKI resistance, and discusses the factors that clinicians should consider when making a second-line treatment choice.

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Introduction

Imatinib was the first *BCR-ABL1* tyrosine kinase inhibitor (TKI) approved (FDA) to treat chronic myeloid leukemia (CML).[1] In the phase III International Randomized Study of Interferon and STI571 (IRIS) in patients with newly diagnosed CML in chronic phase (CML-CP), imatinib had a significant progression-free survival (PFS) advantage (92.1% vs. 73.5%; $P < .001$), as well as significantly higher rates of complete cytogenetic response (CCyR) (76.2% vs. 14.5%; $P < .001$), at 18 months, compared with interferon alfa plus cytarabine.[2] At 60 months, the estimated best cumulative CCyR for imatinib was 87%, and overall survival (OS) rate was 89% (95% confidence interval, 86 to 92).[3] No analysis was conducted in the interferon alfa plus cytarabine group, as only 3% of patients remained on this treatment at 60 months; most patients had switched to imatinib or discontinued therapy.[3] A retrospective analysis comparing outcomes of patients treated with imatinib in the IRIS study and patients treated with interferon alfa plus cytarabine in the French CML91 study[4,5] found a significant OS advantage at 3 years with imatinib (92% vs. 84%; relative risk of death 0.46; $P < .001$).

Although the introduction of imatinib has changed the clinical outlook for patients diagnosed with CML, a proportion of patients treated with first-line imatinib develop resistance to treatment. After 8 years of follow-up of the IRIS study, 45% of patients randomized to imatinib had discontinued treatment, including 16% of patients who cited unsatisfactory therapeutic outcome as the reason for discontinuation. Furthermore, the estimated event-free survival (EFS) at 8 years was 81%,[6] indicating that about a fifth of patients had experienced at least one event (defined as increasing white cell count $> 20 \times 10^9$/L, loss of complete hematologic response [CHR] or major cytogenetic response [MCyR], progression to advanced-stage CML, or death from any cause) during those 8 years.

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Since the approval (FDA) of imatinib in 2001, additional TKI treatment options have been approved, including dasatinib,[7] nilotinib,[8] bosutinib,[9] ponatinib,[10] and omacetaxine.[11] These newer therapies have demonstrated improved response compared with imatinib in the first-line setting and have shown efficacy in second or later lines of therapy, even in patients with resistance to imatinib. Before second-line TKI therapy is initiated, how should clinicians identify patients who are resistant to first-line TKI treatment? How should clinicians choose a second-line treatment option?

With an emphasis on clinical evidence that forms the basis for clinical practice guidelines, this review estimates the rate of TKI resistance that might be expected in the first-line setting, outlines practical approaches to determine TKI resistance, and discusses the factors that clinicians should consider when making a second-line treatment choice.

Incidence of TKI Resistance in the First-line Setting

"Resistance" to imatinib has not been defined uniformly in clinical studies. If "primary resistance" is defined as the failure to achieve a specific level of response by a certain time point and "secondary resistance" as the loss of response or the progression of disease,[12] definitions that are consistent with those of the recently updated National Comprehensive Cancer Network (NCCN) guidelines,[13] then the incidence of resistance to first-line imatinib ranges approximately from 20% to 50% (Table 1)[14-20] (Fig. 1).[2,3,6,21-24]

The potential for patients to develop resistance to imatinib led to the development of more potent TKIs, including dasatinib and nilotinib.[25] These TKIs were approved (FDA) for second-line treatment of CML in 2006 and 2007, respectively, and both were approved for first-line treatment in 2010,[7,8] based on efficacy and safety in phase III clinical studies.

The incidence of resistance to front-line TKI treatment is generally lower with nilotinib and dasatinib than with imatinib, although up to 20% of patients may still be affected (see Table 1). In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study, which used European LeukemiaNet (ELN) 2006 criteria to define suboptimal response to and treatment failure of first-line TKI treatment,[16,26] the incidence of resistance to nilotinib was about half of that to imatinib (see Table 1). ELN 2006 criteria were also used to define disease progression and treatment failure in the Dasatinib vs. Imatinib Study In Treatment-Naïve CML Patients (DASISION) study.[18,26] In that study, the incidence of suboptimal response and treatment failure with dasatinib was about half of that with imatinib, although the incidence of disease progression at 12 months was similar in both treatment arms (see Table 1). It is important to note that recent updates to the ELN guidelines no longer define responses as suboptimal but rather designate suboptimal responses as "warning."[27]

Incidence of Newly Detectable *BCR-ABL1* Kinase Domain Mutations in the First-line Setting

Resistance to TKI therapy can be caused by a number of factors that are not mutually exclusive. Patients whose disease responds inadequately to TKI therapy should be assessed for treatment adherence and potential drug interactions[13] that could affect drug pharmacokinetics. Other patient-related factors, such as activity drug transporters,[28] might affect intracellular drug uptake and bioavailability. Disease-related mechanisms of TKI resistance may include clonal evolution,[14,29] genomic amplification of the *BCR-ABL1* gene,[29] and the development of genetic mutations in the *BCR-ABL1* kinase domain.[29,30] Because extensive data are available, this review will focus on kinase domain mutations, a very common cause of resistance to TKI therapy.

The frequencies at which *BCR-ABL1* kinase domain mutations are detected in the first-line setting are summarized in Table 2. To interpret these data, it is important to note the conditions under which patients had postbaseline mutational analysis done. Some cohorts were selected for mutational analysis because they presented with clinical signs of TKI resistance, such as failure to achieve a certain level of response or loss of response.[14,20,31,32] In these cohorts, it is not surprising that the incidence of newly detected mutations is relatively high, up to 50.0% (see Table 2). Similarly, per protocol, patients in the DASISION study had postbaseline mutational analysis done only upon discontinuation of study treatment. A total of 59 patients (23%) in the dasatinib arm and 64 patients (25%) in the imatinib arm discontinued study treatment, including 22 dasatinib-treated patients and 28 imatinib-treated patients who discontinued because of disease progression or treatment failure (ie, potential signs of resistance). Because of this selection, the incidence of newly detected mutations in those DASISION patients who underwent mutational analysis was relatively high—about 20%.[33] By comparison, nearly all patients in the ENESTnd study had postbaseline mutational analysis done, because the criteria warranting testing (including lack of response, loss of response, and end of therapy for any reason) were relatively permissive. In this study, the incidence of newly detected mutations was relatively low—about 5% among patients treated with nilotinib and 9% among patients treated with imatinib.[34] These observations suggest that new *BCR-ABL1* kinase domain mutations are likely to be detected among patients with clinical signs of resistance, but that the overall incidence of *BCR-ABL1* mutations developing in patients treated with first-line TKI therapy is lower.

The T315I mutation is considered a clinically significant mutation because until recently, patients harboring this mutation had very few treatment options. As summarized in Table 2, among patients with newly detected *BCR-ABL1* mutations, the T315I mutation is observed in 25% of patients. The incidence of this mutation as a proportion of patients treated with TKIs in the first-line setting who underwent mutational testing during the DASISION and ENESTnd trials is 2%. If the criteria for postbaseline mutational testing had been the same in both studies, then the incidence of T315I after first-line nilotinib or dasatinib might have been lower than 2%. This suggests that the T315I mutation, although clinically significant, does not occur frequently among patients with CML treated with first-line TKI therapy.

Identification of Patients With TKI Resistance

At Baseline

Sokal or Hasford risk score at baseline is correlated with response to first-line TKI therapy, with a high risk score at baseline predicting poorer response to first-line TKI therapy than a low risk score.