

# What Is Imatinib-resistant Chronic Myeloid Leukemia? Identifying and Managing Loss of Response

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**Abstract:** Imatinib is widely recognized as the standard of care in the first-line treatment of chronic myeloid leukemia (CML); however, resistance can limit its long-term benefits. Early identification of the loss of response to imatinib is therefore important for the optimal management of patients with this type of leukemia. Cytogenetic and molecular responses during the first 12 months of treatment have been shown to predict future responses (complete cytogenetic response and major molecular response) and reduce disease progression. The degree of early reduction in *BCR-ABL* levels after commencing imatinib therapy is a good indicator of subsequent response. Monitoring for kinase domain mutations should also be considered in patients with suboptimal response or in those who demonstrate resistance. Modification of the treatment strategy is required if there is a loss of response. Dasatinib and nilotinib are the most extensively studied second-generation *BCR-ABL* tyrosine kinase inhibitors, and are currently approved for treating patients following imatinib failure.

The introduction of the *BCR-ABL* inhibitor imatinib (Gleevec, Novartis) represented a major advance in the treatment and prognosis of chronic myeloid leukemia (CML) and is accepted as the standard of care in the first-line treatment of chronic phase CML (CP-CML).<sup>1,2</sup> While response rates are high and durable with imatinib in newly diagnosed CP-CML patients,<sup>3</sup> it should not lead to complacency in the clinical management of CML.<sup>4</sup>

Resistance is a key challenge in the treatment of patients with CML.<sup>1</sup> Best practice for CML management requires proactive consideration of imatinib resistance and implementation of strategies that assess primary resistance and manage loss of response.

Resistance to imatinib in CML patients is an important clinical issue facing community oncologists, and this review examines its impact in clinical practice. The importance of early identification of loss or lack of response to imatinib, the mechanisms of imatinib

## Keywords

imatinib, chronic myeloid leukemia, dasatinib, nilotinib, *BCR-ABL*

**Table 1.** Operational Definition of Failure and Suboptimal Response for Previously Untreated Patients in Early Chronic Phase Chronic Myeloid Leukemia Treated With Imatinib 400 mg/day<sup>7</sup>

Time After Diagnosis (months)	Failure	Suboptimal Response
3	No HR (stable disease or disease progression)	Less than CHR
6	Less than CHR, no CyR (Ph+ >95%)	Less than PCyR (Ph+ >35%)
12	Less than PCyR (Ph+ >35%)	Less than CCyR
18	Less than CCyR	Less than MMR
Anytime	Loss of CHR*, loss of CCyR <sup>†</sup> , mutation <sup>‡</sup>	ACA in Ph+ cells <sup>§</sup> , loss of MMR <sup>§</sup> , mutation <sup>§</sup>

ACA=additional chromosome abnormalities; CHR=complete hematologic response; CCyR=complete CyR; CyR=cytogenetic response; HR=hematologic response; MMR=major molecular response; PCyR=partial CyR; Ph+=Philadelphia chromosome positive.

\*To be confirmed on 2 occasions unless associated with progression to accelerated phase or blast crisis phase; <sup>†</sup>To be confirmed on 2 occasions unless associated with CHR loss or progression to accelerated phase or blast crisis phase; <sup>‡</sup>High level of insensitivity to imatinib; <sup>§</sup>To be confirmed on 2 occasions unless associated with CHR or CCyR loss; <sup>§</sup>Low level of insensitivity to imatinib.

resistance, and strategies to manage loss of response, as well as best practice recommendations are also discussed.

### Imatinib Resistance in Clinical Practice

Resistance limits the long-term benefits of imatinib. The rates of relapse and resistance appear to correlate with disease stage<sup>5</sup> and the incidence increases as CML progresses.<sup>6</sup> Resistance to imatinib in CML is defined as either primary (intrinsic) or secondary (acquired) resistance (relapse). Primary resistance is a lack of efficacy from the onset of treatment with imatinib, and secondary resistance is defined as the loss of an initial response<sup>5</sup> and includes progression to advanced-phase disease during treatment.

Patients can be classified according to their response to treatment, which can be considered optimal, suboptimal, or failure (Table 1).<sup>2,7,8</sup> Failure indicates that primary resistance patients in this category should be switched to another treatment. Patients in the suboptimal category may still benefit from continued treatment with imatinib, but a favorable long-term outcome is not probable at the current dose.

Although primary resistance is perceived to be rare in early CP-CML, the problem should not be underestimated. While only approximately 5% of newly diagnosed patients do not achieve a complete hematologic response (CHR) with imatinib, 16% fail to achieve a major cytogenetic response (MCyR) with imatinib at 12 months and 24% fail to achieve a complete cytogenetic response (CCyR) at 18 months (See Table 2 for response definition).<sup>3,9</sup> Thus, approximately one-quarter of newly diagnosed patients demonstrate some evidence of primary resistance to 400 mg/day of imatinib.<sup>4</sup> Furthermore, the frequency of primary hematologic resistance increases with the disease phase (Figure 1).<sup>5</sup> As mentioned above, patients with suboptimal response to standard-dose imatinib may require a different therapy. Clinical studies are ongoing in patients with suboptimal response to determine the most appropriate time to switch treatment.

Secondary resistance is defined as a loss of hematologic, cytogenetic, or molecular response, as well as progression to advanced phases of CML. This clinical issue represents an increasing challenge for community oncologists. Additionally, although relapse rate is lower among patients who achieve a CCyR,<sup>11</sup> residual malignant progenitors may present a persistent risk of relapse even with long-term therapy.<sup>12</sup> While certain properties—such as Sokal/Hasford score, organic cation transporter (OCT)-1 expression, and the presence of additional chromosomal abnormalities (eg, del[9q])—can be helpful in identifying patients who are at greater risk of developing resistance to imatinib,<sup>13</sup> there are currently no tests that can reliably predict resistance at the time of diagnosis.

A review of the prognosis of 420 patients with CML who experienced imatinib failure demonstrated that survival rates were low in those whose disease progressed into the accelerated (AP) and blastic phases (BP).<sup>14</sup> Estimated 3-year survival rates were as follows: 72% in CP-CML; 30% in AP; and 7% in BP. This study not only highlights the need for improved treatment for patients with imatinib-resistant disease, but also the importance of timely identification of resistance in order to ensure that patients receive the most appropriate therapy as early in the disease course as possible.

### Early Identification of Loss of Response to Imatinib

Given the approval of the second-generation tyrosine kinase inhibitors (TKI), dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis), and the development of other agents that are active in imatinib-resistant disease, more intensive monitoring of response to imatinib may be prudent. Advances in monitoring

**Table 2.** Definitions of Hematologic, Cytogenetic, and Molecular Response and Resistance<sup>5,7,10</sup>

Response Level/Resistance	Definition
<b>Hematologic</b>	
Complete hematologic response	Platelet count <450 × 10 <sup>9</sup> /L; white blood cell count <10 × 10 <sup>9</sup> /L; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen
Hematologic resistance (chronic-phase CML)	Lack or loss of normalization of peripheral blood counts, differential leukocyte count and spleen size
Hematologic resistance (advanced-phase CML)	Lack of return to chronic phase or hematological relapse after initial response
<b>Cytogenetic</b>	
Complete cytogenetic response	0% Ph+ metaphases
Major cytogenetic response	0–35% Ph+ metaphases
Partial cytogenetic response	1–35% Ph+ metaphases
Minor cytogenetic response	35–65% Ph+ metaphases
Minimal cytogenetic response	66–95% Ph+ metaphases
No cytogenetic response	>95% Ph+
Cytogenetic resistance	Defined according to level of cytogenetic response
<b>Molecular (response defined as BCR-ABL to control gene ratio according to International Scale)</b>	
Complete molecular response	Transcript nonquantifiable and nondetectable
Major molecular response	≤.10
Molecular resistance	Lack or loss of complete molecular response

CML=chronic myeloid leukemia; Ph+=Philadelphia chromosome positive.

Based on definitions from Hochhaus et al<sup>5</sup>, Baccarani et al<sup>7</sup>, and Deininger M.<sup>10</sup>

technology have improved the ability to detect treatment failure at earlier time points.

Real-time quantitative polymerase chain reaction (qPCR) for measuring *BCR-ABL* levels in peripheral blood should become standard for monitoring patients on imatinib for a number of reasons:<sup>15,16</sup> this methodology identifies the degree of molecular response and predicts long-term outcomes; provides an early indication of relapse and imatinib resistance; detects residual leukemia below the limits of detection with bone marrow cytogenetic analysis; and can reduce the need for regular bone marrow biopsies. However, despite these advantages, the technical complexities associated with this technology, allied with the associated costs of qPCR, need to be addressed.

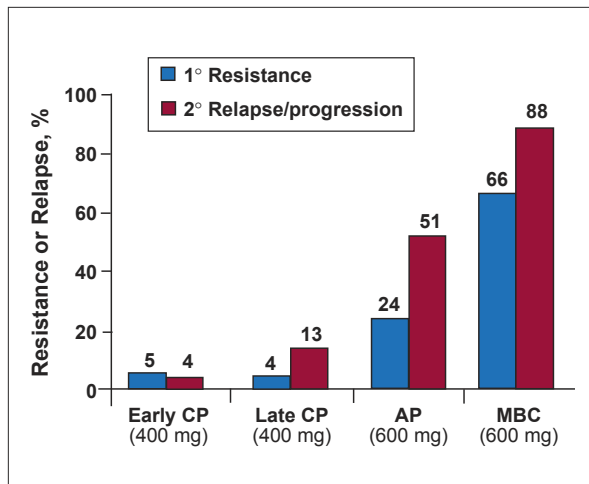
**Clinical Value of BCR-ABL Monitoring**

The value of qPCR monitoring is illustrated by looking at the results from the IRIS (International Randomized

study of Interferon vs STI-571) trial, which showed that *BCR-ABL* levels correlate with progression-free survival.<sup>4</sup>

Of the patients with a CCyR or partial cytogenetic response (PCyR) at 12 months, an estimated 97% and 93%, respectively, did not progress to the AP or BP by 60 months (*P*=.20, CCyR vs PCyR).<sup>11</sup> In comparison, the estimate was 81% for those patients who did not achieve a MCyR (which includes CCyR and PCyR) at 12 months (*P*<.001). Patients with a CCyR at 12 months without a major molecular response (MMR), defined as greater than 3 log reduction in *BCR-ABL/BCR* level compared with the median pretreatment level, had a higher risk of progression than those who achieved CCyR and MMR (8% vs 0% with 2-year follow up).<sup>4</sup>

The use of “log reduction” terminology in the IRIS trial has led to some degree of confusion as it seems to imply that the value is a relative reduction from the patient’s actual baseline.<sup>7</sup> In the IRIS trial and subsequent analyses, the baseline transcript level used to calculate



**Figure 1.** Frequency of hematologic primary resistance and relapse/progression according to chronic myeloid leukemia disease phase after 2 years of therapy with imatinib.<sup>5</sup>

AP=accelerated phase; CP=chronic phase; MBC=myeloid blast crisis.

the log reduction is actually a predetermined median value established from a small cohort of samples from untreated CML patients.<sup>11</sup> Therefore, it is not necessary to obtain the actual baseline level of a particular patient in order to calculate the log reduction in that patient.<sup>4</sup>

A qPCR sub-study was conducted in Australian patients from the IRIS trial, measuring the leukemic load irrespective of cytogenetic response in each patient at 3- or 6- month intervals.<sup>4</sup> This work showed that the degree of reduction in *BCR-ABL* levels achieved early after starting imatinib therapy is a good indicator of subsequent response. Those patients who did not achieve a 1-log reduction by 3 months had a very low probability of achieving a MMR (Figure 2).<sup>4</sup> There was a high estimated risk of resistance (83%) in this group; failure to achieve a MMR was mainly due to primary and acquired resistance (Figure 3).<sup>4</sup> Further, a rise in *BCR-ABL* levels detected by qPCR is an early indication of loss of response, and is highly associated with *BCR-ABL* mutations.<sup>17</sup>

While early detection is desired to optimize treatment outcomes, it remains challenging due to variable kinetics of response, greater significance of ultimate level of response rather than speed, and a concern that inadequate response could be “overcalled.”<sup>8</sup> qPCR methods for *BCR-ABL* at this stage are not standardized internationally and each laboratory will need its own criteria for acceptable RNA quality, sensitivity, precision, and level of significance.<sup>18</sup>

### Indications for Mutation Analysis

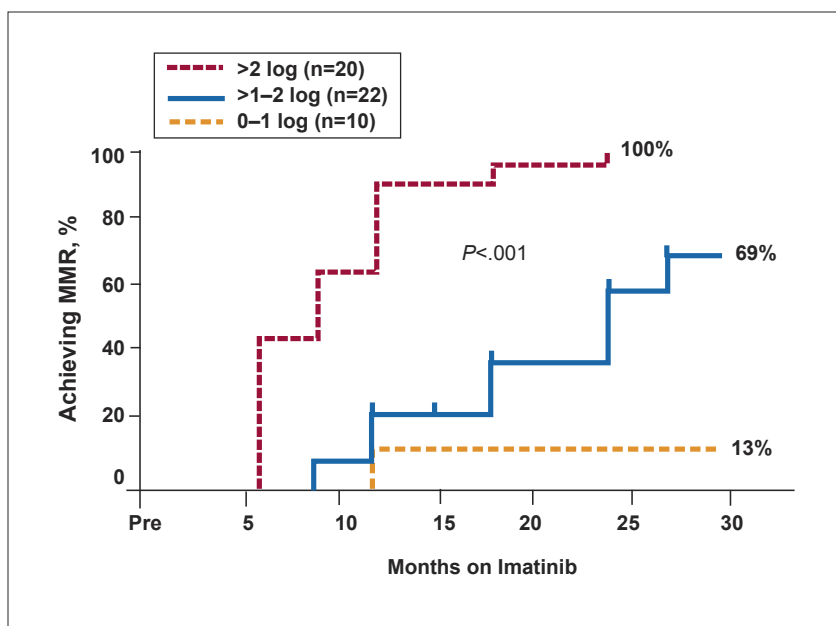
While primary resistance to imatinib in patients with CML is rarely, if ever, caused by point mutations in the kinase domain of the *BCR-ABL* gene, 35–90% of cases with acquired resistance are caused by point mutations.<sup>4</sup> Approximately 50 *BCR-ABL* mutations associated with imatinib resistance have been identified,<sup>1,19</sup> but many of these are relatively rare. The most common affect the P-loop (amino acids 248–255), T315, M351, and F359V.<sup>20,21</sup> The frequency of mutations increases as CML progresses, highlighting the importance of monitoring patients, allowing an early change in treatment strategy before CML becomes resistant to alternative therapies. Community oncologists should consider monitoring for kinase domain mutations, as it provides essential information to guide clinical management.<sup>4,22</sup>

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for CML recommends routine mutational screening (every 3 months) in patients with advanced-phase disease regardless of treatment response. For patients in CP, screening for *ABL* kinase domain mutations is recommended if there is a suboptimal response or any sign of a loss of response, as denoted by hematologic or cytogenetic relapse.<sup>2</sup> Additionally, several studies have demonstrated an association between rising *BCR-ABL* transcript levels and the presence of a mutation. Branford and colleagues showed that among patients with a two or higher fold increase in *BCR-ABL* transcript ratio, 61% (34/56) had a detectable mutation.<sup>17</sup> Results from another study suggested that a serial rise ( $\geq 2$ -fold) in transcript levels on at least two separate occasions was a more reliable predictor than a single transcript rise of two or higher fold.<sup>23</sup> Despite the somewhat conflicting conclusions of these studies, the findings collectively indicate that a rise in *BCR-ABL* transcript level should, indeed, prompt a mutational screening.<sup>2</sup>

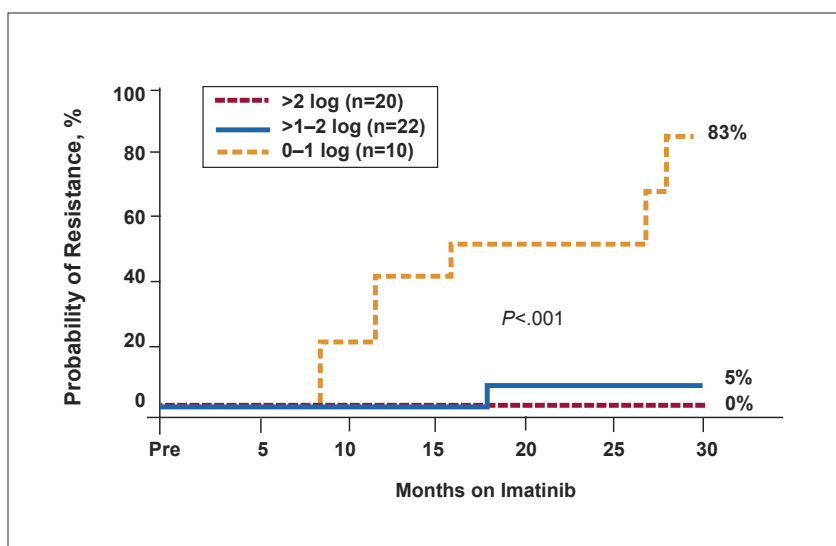
### Understanding the Mechanisms of Imatinib Resistance to Develop New Treatment Approaches

Secondary resistance is most often caused by *BCR-ABL* mutations that prevent imatinib binding to its target.<sup>24</sup> This finding highlights the need for agents with improved binding characteristics.<sup>25</sup> The activation loop (A-loop) and the ATP-binding loop (P-loop) of the *ABL*-kinase are critical for catalysis,<sup>10</sup> and mutations in the P-loop are associated with a poorer prognosis in patients receiving imatinib.<sup>26</sup> Second generation *BCR-ABL* inhibitors, such as dasatinib and the imatinib analog, nilotinib, are effective against the majority of imatinib-resistant mutations. However, nilotinib may be less effective against P-loop

**Figure 2.** Probability of achieving a major molecular response (MMR) dependent on the log reduction of *BCR-ABL* (from the standardized baseline at 3 months of imatinib treatment).<sup>4</sup>



**Figure 3.** Probability of primary or acquired resistance to imatinib dependent on the log reduction of *BCR-ABL* (from the standardized baseline at 3 months of imatinib treatment).<sup>4</sup>



mutations, as in vitro assays demonstrated an increase in  $IC_{50}$  of up to 39-fold against such mutations.<sup>27</sup> It should be noted that the P-loop comprises a heterogeneous group of mutations, each with a specific level of resistance. Among them, the Y253H and E255V mutations appear to confer the highest level of resistance.<sup>27</sup> Additionally, the T315I mutation confers complete resistance to all of the TKIs currently available for clinical use.

Reactivation of BCR-ABL signaling is an important mechanism in acquired resistance to imatinib<sup>10</sup> that

emphasizes the need to use agents that target BCR-ABL. In addition, other pathways (eg, the SRC family kinases [SFKs]) may be important in CML progression<sup>28</sup> and may also be responsible for BCR-ABL-kinase independent resistance to imatinib. This finding provides the rationale for investigating inhibitors that target multiple kinase pathways; for example, dasatinib targets *BCR-ABL* and SFKs.<sup>28</sup> Another putative mechanism of imatinib resistance involves altered expression of transporter proteins that affect intracellular drug concentrations,

such as OCT-1, Permeability-glycoprotein (Pgp), and ATP-binding cassette G2.<sup>29</sup> Indeed, clinical studies have shown an association between intracellular drug levels and molecular responses to imatinib.<sup>30,31</sup> In the absence of a clinical assay for intracellular levels of imatinib, blood level testing is currently being investigated as a means to help optimize treatment that is based on an association between low imatinib plasma levels and reduced response rates.<sup>32</sup> In contrast to imatinib, it appears that some second generation TKIs are not affected by the activity of these transporters. For example, dasatinib is not a substrate for Pgp, and its intracellular accumulation is not limited by expression of this protein.<sup>33,34</sup> Additionally, White and associates showed that intracellular accumulation of the imatinib analog, nilotinib, is not dependent on OCT-1-mediated influx.<sup>35</sup> Therefore, these agents may overcome imatinib-resistance induced by altered expression of transporter proteins.

Another possible mechanism is CML stem cell resistance, with evidence that the most primitive CML cells remain resistant to imatinib as well as nilotinib and dasatinib.<sup>36,37</sup> These observations, combined with the excellent and sustained disease control observed with imatinib therapy in the majority of CML patients, suggest that significant disease load reduction below a critical level to prevent disease progression might be a more realistic goal than disease eradication.

## Compliance

As with other oral anti-cancer agents, particularly long-term treatments for asymptomatic patients with chronic disease,<sup>38</sup> nonadherence to the prescribed treatment regimen is a concern with imatinib. Numerous factors can influence patient compliance, including age,<sup>38</sup> psychologic variables,<sup>39</sup> and a patient's understanding of the risk of nonadherence.<sup>39</sup> Adherence can be substantially affected by the incidence and severity of adverse events.<sup>40,41</sup> Findings from a retrospective analysis evaluating claims in the HealthCore Managed Care Database showed that of 29% (62/216) of patients in whom imatinib therapy was suspended and/or permanently discontinued, the most frequent causes were anemia (11%) and thrombocytopenia (11%).<sup>41</sup> Additionally, Sun and coauthors showed that adherence rates decrease with increased doses of imatinib (600 to  $\geq 800$  mg/day).<sup>42</sup> These results correlate with the greater incidence and severity of adverse events that are known to occur with higher doses of imatinib.<sup>43</sup> Furthermore, it has also been shown that patients are more adherent to treatment with fewer dosing frequencies per day.<sup>39,44</sup> The results of Sun and coauthors may also be reflective of this latter effect, given that imatinib 800 mg/day is administered as

400 mg twice daily compared with the once daily administration of 400–600 mg/day.<sup>42,45</sup>

Poor adherence can impede the achievement of treatment goals and may result in disease progression,<sup>39</sup> highlighting the importance of ensuring compliance with the prescribed treatment regimen. Monitoring the plasma levels of imatinib may assist in identifying nonadherence among patients treated with imatinib. If low imatinib plasma levels are detected, clinicians should engage in a discussion with patients to explain the importance of adhering to the prescribed treatment regimen and to determine the reason for nonadherence. It is possible that such patients are nonadherent due to imatinib intolerance, and would benefit from a change in treatment to either dasatinib or nilotinib.

## Strategies to Manage Loss of Response to Imatinib

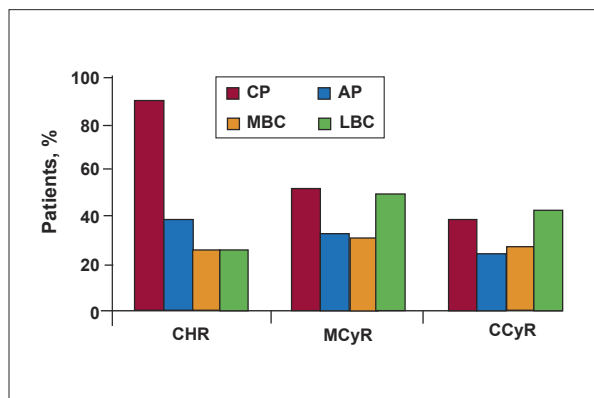
There are currently three treatment options recommended for patients who are not responsive to imatinib. Allogeneic stem cell transplantation (SCT) remains a valid treatment option after failure of imatinib, but is limited by donor availability<sup>5</sup> and discouraged by transplant-related morbidity.<sup>46</sup> Additionally, two TKI-based therapies have undergone significant clinical evaluation following failure of imatinib 400 mg/day.

### *Modification of the Imatinib Regimen*

Dose escalation of imatinib (600–1000 mg/day) can overcome resistance to standard-dose imatinib (400 mg/day) in some patients with CML.<sup>47–49</sup> However, the responses were of a short duration, with only 19% of patients achieving a CCyR in one study<sup>49</sup> and less than 20% in another study of patients with late CP-CML, and associated with more hematologic toxicity.<sup>47,50</sup> In the case of P-loop mutations, escalation of the dose of imatinib is not recommended due to the highly resistant nature of these mutations. Additionally, it is possible that this treatment will only benefit patients who have suboptimal intracellular drug levels with standard-dose imatinib.

### *Dasatinib*

Dasatinib is currently the only Food and Drug Administration–approved TKI therapy for the treatment of patients with imatinib-resistant or -intolerant CML or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). This agent is a novel, orally available, multitargeted kinase inhibitor with potent activity against BCR-ABL and SFKs. Dasatinib is 325-fold more potent against BCR-ABL than imatinib in vitro,<sup>27</sup> and has shown activity, although somewhat reduced, against all imatinib-resistant mutants, except T315I.<sup>27,51</sup>



**Figure 4.** Summary of data from the dasatinib phase II clinical trial program.<sup>56-58</sup> Please note that the higher percentages of cytogenetic responses, when compared to hematologic responses, stem from the cytopenias associated with dasatinib treatment.

AP=accelerated phase; CCyR=complete cytogenetic response; CHR=complete hematologic response; CP=chronic phase; LBC=lymphoid blast crisis; MBC=myeloid blast crisis; MCyR=major cytogenetic response.

Importantly, dasatinib appears to maintain a high level of potency against BCR-ABL with mutations of the P-loop,<sup>27</sup> and it is believed that interactions within this region are not as critical for binding of dasatinib to the ABL kinase as compared with imatinib.<sup>25</sup> Additionally, the anti-SRC activity of dasatinib may also contribute to its efficacy following imatinib failure, as SFKs have been implicated in imatinib resistance and leukemic progression.<sup>28,52-55</sup>

Dasatinib showed impressive efficacy in a series of open-label, phase II clinical trials with high rates of CCyR observed in imatinib-resistant or -intolerant patients with all phases of CML and Ph+ ALL (Figure 4). Furthermore, the rate of response among CP patients was similar between those with native and mutant *BCR-ABL*, including patients harboring P-loop mutations;<sup>56-59</sup> albeit, somewhat reduced in patients with an E255K/V P-loop mutation.<sup>60</sup> CCyRs were observed in 8 of 24 (33%) patients with E255/V mutations, which is only slightly lower than that of the other P-loop mutations.<sup>60</sup> Dasatinib was generally well tolerated, and nonhematologic adverse events were generally mild-to-moderate in severity. Cytopenias and pleural effusions were effectively managed with dose modification. Additionally, steroid treatment has also been used for managing pleural effusions in some cases.<sup>61</sup>

In a randomized study comparing dasatinib (70 mg twice daily) with dose-escalated imatinib (800 mg/day) in patients with imatinib-resistant CP-CML, dasatinib has shown superior efficacy. With a median follow-up of 15 months, dasatinib induced MCyRs in 52% of patients

compared to 33% with imatinib ( $P=.023$ ). Moreover, CCyRs were achieved in a significantly greater number of patients receiving dasatinib versus imatinib (40% vs 16%;  $P=.004$ ), and the MMR rate was also improved with dasatinib (16% vs 4%;  $P=.038$ ). Dasatinib also resulted in significantly better CCyR rates than dose-escalated imatinib in the subgroup of patients who had received prior imatinib treatment at 600 mg/day (38% vs 6%;  $P=.0006$ ). In the subgroup of patients who received prior imatinib at 400 mg/day, MCyR rates favored dasatinib (58% vs 53%), but the difference was not statistically significant.<sup>59</sup> The greater efficacy of high-dose imatinib among patients who had prior treatment with 400 mg/day imatinib compared with those pretreated with 600 mg/day is perhaps not surprising, given that the relative dose increases in these patients were 100% and 33%, respectively.

Subsequent to the initial approval of dasatinib 70 mg twice daily for the treatment of imatinib-resistant or -intolerant patients with CML in any phase or Ph+ ALL (June 2006), the optimal dose for patients with CP-CML was evaluated in a phase III, randomized trial. Patients with CP-CML who were resistant to or intolerant of imatinib ( $n=670$ ) were randomly assigned to one of four dasatinib dosing regimens: 100 mg once daily ( $n=167$ ); 50 mg twice daily ( $n=168$ ); 140 mg once daily ( $n=167$ ); or the previously approved starting dose, 70 mg twice daily ( $n=168$ ). With a minimum of 6 months of follow-up, hematologic and cytogenetic response rates were similar across the four arms and were consistent with those demonstrated in the phase II trial program.<sup>58,59</sup> However, fewer pleural effusions and grade 3/4 cytopenias were experienced on the 100 mg once-daily regimen compared with the other dosing schedules.<sup>62</sup> Based on these results, it was concluded that the 100 mg once-daily regimen offered a better risk-benefit ratio than the previously approved 70 mg twice-daily regimen. The findings from this trial prompted a change in the recommended starting dose for patients with CP-CML to 100 mg once daily, which is included in the November 2007 update to the dasatinib prescribing information.<sup>62</sup> This newly approved dose is also expected to improve treatment adherence compared with the previously approved twice-daily dose, given that patients should experience fewer serious adverse events, and that the once-daily schedule offers the convenience of fewer administrations per day. It should be noted that the recommended starting dose for patients with advanced-phase disease is 70 mg twice daily.<sup>62</sup>

### Nilotinib

Nilotinib is an analog of imatinib with similar targets, including BCR-ABL, platelet-derived growth factor receptor, c-Kit, and ephrin B4; however, it does not have activity against SRC.<sup>27,63,64</sup> Like dasatinib, nilotinib

has demonstrated *in vitro* activity against most imatinib-resistant *BCR-ABL* mutations, except T315I<sup>65</sup>; although, as mentioned previously, its activity is diminished against certain mutations, such as those within the P-loop.<sup>27</sup> This agent is now approved for the treatment of patients with CP- or AP-CML who are resistant to or intolerant of imatinib. In phase II clinical trials, nilotinib showed impressive activity in patients with imatinib-resistant or -intolerant CML (Figure 5).<sup>66</sup> However, consistent with the *in vitro* studies, fewer CCyRs were achieved in patients with P-loop mutations at baseline as compared to those without these mutations. Of 20 patients with CP-CML who had P-loop mutations, only 1 (8%) achieved a CCyR, compared with 23% and 35% of patients harboring any mutation and no mutation, respectively. Therefore, further studies may be necessary to determine whether nilotinib is appropriate for the treatment of such patients.

### Allogeneic SCT

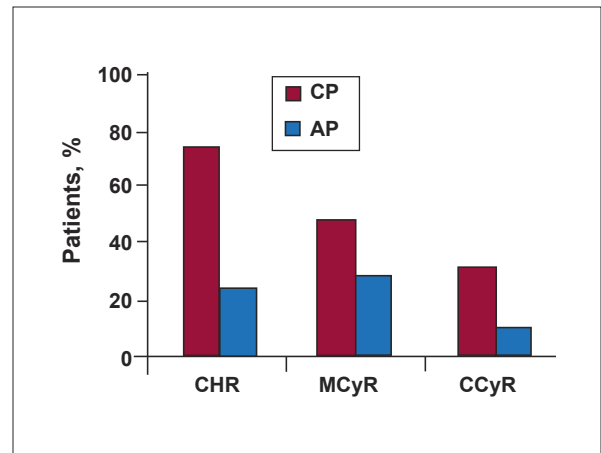
Allogeneic SCT remains the only potentially curative therapy for patients with CML, although it is associated with early morbidity and mortality. The 10-year survival rate with SCT when performed in CP is approximately 75%. However, as with other treatment modalities, the outcome is substantially inferior in patients treated after progression to advanced-phase disease.<sup>68,69</sup> In a small series of 9 imatinib-resistant CML patients (3 in CP, 4 in AP, 2 in BP) who were subsequently treated with allogeneic SCT, 7 patients were alive after a median follow-up of 19 months (6 in complete molecular response and 1 in MMR).<sup>70</sup> Thus, SCT can be considered in patients with suboptimal response or patients who relapse, optimally before disease progression.

### Future Options

There is strong preclinical evidence suggesting that combining imatinib and nilotinib or imatinib and dasatinib has synergistic effects and could circumvent resistance. Nevertheless, these observations will need confirmation in clinical studies. In addition, none of the studied combinations seem active against the T315I mutation.<sup>71,72</sup>

Other TKIs are currently in earlier stage clinical trials, including the dual SRC/BCR-ABL inhibitors SKI-606 and INNO-406.<sup>73-75</sup> Like the other second-generation BCR-ABL inhibitors, these agents have greater potency against native BCR-ABL compared with imatinib and efficacy in a majority of imatinib-resistant BCR-ABL mutations. However, they remain ineffective against the T315I mutation, which highlights the need for agents that are active against this mutation.<sup>74</sup>

Agents aimed at overcoming T315I-mediated resistance are in development, such as the aurora kinase



**Figure 5.** Summary of clinical data from the nilotinib clinical trials program.<sup>66,67</sup>

AP=accelerated phase; CCyR=complete cytogenetic response; CHR=complete hematologic response; CP=chronic phase; MCyR=major cytogenetic response.

inhibitor MK-0457.<sup>76-79</sup> Recently reported results from a clinical trial showed that MK-0457 induced responses in 3 patients with CML or Ph+ ALL harboring the T315I mutation.<sup>77</sup> This agent is the first TKI to show activity in patients with T315I-positive disease. Non-TKI-based therapy may also be effective in treating disease harboring the T315I mutation. The cephalotaxus alkaloid homoharringtonine inhibits protein synthesis and induces apoptosis in malignant cells. In early-phase clinical studies, this agent showed activity in patients with CML that is resistant to TKI-based therapy, including disease harboring the T315I mutation.<sup>80,81</sup> A phase II clinical study of homoharringtonine has been initiated in patients with imatinib-resistant, T315I-positive CML. These agents, if used in combination with other TKIs, could help prevent T315I-mediated disease relapse. Interferon may be an option for patients with T315I-mediated resistance if SCT is unsuccessful or experimental agents are unavailable.

### Summary of Best Practice Recommendations to Manage Imatinib Failure

According to the recommendations outlined by the NCCN, first-line therapy with imatinib (400 mg/day) must be changed if patients fail to achieve a CHR after 3 months; CyR after 6 months; MCyR after 12 months (<35% Ph+); or a CCyR after 18 months (0% Ph+).<sup>2</sup> Some authors have suggested that more stringent therapeutic goals may be appropriate for certain patients treated with

first-line imatinib. For example, failure to achieve MCyR by 6 months was defined as primary resistance by Hughes and coworkers.<sup>4</sup> MMR has emerged as a new treatment goal and is gaining acceptance as a surrogate for long-term benefit in clinical trials.<sup>8</sup> Mauro and Deininger proposed that achieving a MMR by 12 months should be considered optimal since patients who achieve such responses have no risk of disease progression at 54 months.<sup>82</sup> However, in the IRIS trial, patients with both a CCyR and a MMR after 18 months of treatment had an estimated 100% survival at 60 months without disease progression.<sup>3</sup> These results suggest that achieving a MMR may be of greater significance than the time at which the response is achieved.

Imatinib dose escalation may be considered in some patients who experience a loss of response on 400 mg/day imatinib or in those with low imatinib plasma levels. Treatment should be changed to dasatinib or nilotinib if a response is lost in patients who received higher doses of imatinib (ie, 600–800 mg/day) or if imatinib-resistant mutations emerge. Patients whose disease progresses from CP to AP or BP during imatinib treatment should be treated with dasatinib, followed by an allogeneic transplant, if feasible.<sup>2</sup> Once a CCyR is achieved, frequent monitoring of *BCR-ABL* should be conducted (preferably every 3 months) to detect loss of response to imatinib. As rising levels of *BCR-ABL* may be associated with increased risk of acquiring imatinib-resistant mutations, a 1-log increase should prompt mutation analysis, cytogenetic evaluation, and more frequent monitoring of *BCR-ABL* levels. Currently there are no guidelines for changing therapy based on rising *BCR-ABL* transcripts as detected by qPCR, and changes in therapy based solely on a rising *BCR-ABL* level should be done under the auspices of a clinical trial.<sup>2</sup>

## Conclusion

Resistance to imatinib in CML is an important clinical issue facing community oncologists. With the recent approval of dasatinib and nilotinib and the development of other treatments for patients following imatinib failure, timely identification of imatinib resistance becomes increasingly important to ensure that patients receive appropriate therapy as early in the disease course as possible. Best practice strategies should be implemented to guide decisions on whether to continue treatment with imatinib or to change to an alternative therapy.

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