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Long-Term Outcomes in the Second-Line Treatment of Chronic Myeloid Leukemia:

A Review of Tyrosine Kinase Inhibitors

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Abstract

Chronic myeloid leukemia (CML) is a progressive and often fatal myeloproliferative neoplasm. The hallmark of CML is an acquired chromosomal translocation known as the Philadelphia chromosome (Ph), which results in the synthesis of the breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion oncoprotein, a constitutively active tyrosine kinase. The introduction of imatinib, a tyrosine kinase inhibitor (TKI) that is specific for BCR-ABL, was a major breakthrough in CML therapy. Although most patients respond to first-line imatinib therapy, some experience loss of response (resistance) or require treatment discontinuation because of toxicity (intolerance). For patients with CML, failure on standard-dose imatinib therapy (400 mg daily), imatinib dose escalation (600–800 mg daily) is a second-line option. However, high-dose imatinib is not an appropriate approach for patients who experience drug toxicity, and there remain questions over the durability of responses achieved with this strategy. Alternative second-line options include the TKIs dasatinib and nilotinib. A substantial amount of long-term data for these agents is available. Although both are potent and specific BCR-ABL TKIs, dasatinib and nilotinib exhibit unique pharmacologic profiles and response patterns relative to different patient characteristics, such as disease stage and BCR-ABL mutation status. To optimize therapeutic benefit, clinicians should select treatment based on each patient's historic response, adverse-event tolerance, and risk factors.

Keywords

chronic myeloid leukemia; dasatinib; imatinib; nilotinib; second-line therapy

Chronic myeloid leukemia (CML) is a progressive and often fatal myeloproliferative neoplasm with an incidence of approximately 1 to 2 cases per 100,000 adults.[1] The natural history of CML consists of 3 distinct stages: an initial chronic phase (CP), an intermediate accelerated phase (AP), and a terminal blast phase (BP).[2] Most patients (90%) present with

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CONFLICT OF INTEREST DISCLOSURES

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CML in CP, which is a relatively slowly progressing stage characterized by well differentiated leukemic cells.[3,4] AP follows CP and involves poor control of white blood cell counts and increasing numbers of immature blasts in the peripheral blood.[4] After 1 to 2 years, AP transitions into BP, resulting in cytopenias, infections, bleeding, organ failure, and death.[4] Approximately 66% of patients with CP eventually go on to develop BP,[5] and the transition occurs as rapidly as 3 years in the absence of treatment.[2] The median survival for patients with untreated BP CML is 3 to 6 months.[4]

The hallmark of CML is an acquired mutation, initially described in 1960, called the Philadelphia chromosome (Ph).[6,7] This mutation results in a balanced translocation between the Abelson murine leukemia (*ABL*) gene of chromosome 9 and the breakpoint cluster region (*BCR*) gene of chromosome 22 (t[9;22][q34;q11]).[3] In virtually all cases, the resultant BCR-ABL gene encodes a fusion protein.[3] The *BCR-ABL* fusion protein contains a constitutively active tyrosine kinase region of ABL that deregulates cell growth, motility, angiogenesis, and apoptosis, leading to the development of leukemia.[8]

The transition from CP to advanced stages is not well understood but is believed to involve escalating genetic instability.[4] The increased rate of cellular proliferation elicited by BCR-ABL may result in the acquisition of additional chromosomal abnormalities, a process known as clonal evolution.[3,4] The prevalence of clonal evolution increases with advancing CML stage, rising from 30% in AP to as much as 80% in BP.[9]

Given the central role of BCR-ABL in the pathogenesis of CML, inhibiting BCR-ABL tyrosine kinase activity through targeted therapies represents a viable therapeutic strategy.[4] The advent of tyrosine kinase inhibitors (TKIs) designed to abrogate the oncogenic function of BCR-ABL has greatly improved the treatment of CML judged against the historically used interferon-alpha (IFN-α) treatment.[4] Before the introduction of TKIs, IFN-α was the therapy of choice for CML despite the limited durability of responses (complete cytogenetic responses [CCyR] were maintained in just 5% to 25% of patients using this therapy).[10]

TKIs are orally administered agents that compete with adenosine triphosphate (ATP) for its binding site on ABL, leading to inhibition of tyrosine phosphorylation of the proteins involved in BCR-ABL signal transduction and ultimately resulting in apoptosis of the cancer cell.[11–13] The first TKI to be approved by the US Food and Drug Administration (FDA) for the first-line treatment of CML was imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corporation, East Hanover, NJ).[4] Imatinib is indicated for patients with newly diagnosed, Ph-positive CML in CP and for patients with Ph-positive CML in BP, in AP, or in CP after failure on IFN-α therapy.[14] Recommended doses depend on the CML phase: Imatinib 400 mg daily is approved for patients with CP CML, whereas imatinib 600 mg daily is approved for patients with CML in AP or BP.

The clinical activity of imatinib was demonstrated in the pivotal phase 3 International Randomized Study of Interferon Versus STI571 (IRIS) trial, which compared imatinib with IFN-α plus low-dose cytarabine in 1106 patients with newly diagnosed CML in CP.[10] Imatinib, versus IFN-α plus cytarabine, yielded significantly better rates of a major cytogenetic response (major cytogenetic response [MCyR] rate, 87% vs 35%; $P < .001$) and

CCyR (76% vs 14%; $P < .001$) after 18 months of treatment. The progression-free survival (PFS) rate for patients with CML in AP or BP also was significantly better with imatinib compared with IFN-α plus cytarabine (97% vs 91%; $P < .001$). Responses with imatinib were durable. At 8 years of follow-up, the event-free survival rate was 81%, The PFS rate for patients with CML in AP or BP was 92%, and the estimated overall survival (OS) rate at 8 years was 85% (93% when only CML-related deaths and deaths before stem cell transplantation [SCT] were considered).[15] Imatinib was well tolerated, and the adverse events were mostly mild or moderate in intensity. After a median follow-up of 60 months, the most commonly reported adverse events were edema (including peripheral and periorbital edema; 60%), nausea (50%), muscle cramps (49%), musculoskeletal pain (47%), diarrhea (45%), rash and other skin problems (40%), fatigue (39%), abdominal pain (37%), headache (37%), and joint pain (31%).[16] Grade 3 or 4 adverse events consisted of neutropenia (17%), thrombocytopenia (9%), anemia (4%), and elevated liver enzymes (5%).[16] Although first-line imatinib therapy is tolerated well, patients should be monitored for potential serious adverse events, such as edema and severe fluid retention, hematologic toxicity, congestive heart failure, and hepatotoxicity.[14]

Some patients who are receiving imatinib experience primary (intrinsic) or secondary (acquired) resistance.[4] Primary resistance has been defined as the failure to achieve a landmark response after starting treatment.[17] According to the National Comprehensive Cancer Network (NCCN) guidelines, primary resistance is defined as the failure to achieve hematologic remission within 3 to 6 months of treatment initiation, any level of cytogenetic response at 6 months, an MCyR at 12 months, or a CCyR at 18 months.[18] The European LeukemiaNet (ELN) recommendations define treatment failure similarly as less than hematologic remission within 3 months, no cytogenetic response within 6 months, less than a partial cytogenetic response (PCyR) within 12 months, and less than a CCyR within 18 months.[19] In the IRIS trial, primary resistance, as evidenced by a lack of CCyR at 18 months, occurred in 24% of patients.[10] Secondary resistance is defined as disease progression and loss of therapeutic effect while continuing on an imatinib regimen that previously had resulted in a response.[4] In a 5-year follow-up of the IRIS trial, secondary resistance occurred in 24% of patients (recurrence rate, 17%; progression rate, 7%).[16]

Imatinib resistance is attributed to several mechanisms.[20] Point mutations in the *BCR-ABL* oncogene are the most common cause of imatinib resistance, particularly secondary resistance, and occur in 35% to 70% of patients with resistance.[20–22] These mutations can change the conformation of the BCR-ABL protein without significantly impairing its function and may induce a shift in the equilibrium of the BCR-ABL oncoprotein from the inactive form, which imatinib binds, to the active form, which imatinib is unable to bind.[20] BCR-ABL kinase domain mutations can occur either spontaneously or as a result of selective pressure, in which continued imatinib treatment eliminates sensitive leukemic cells and selects for resistant mutant cells. Other possible mechanisms of imatinib resistance include *BCR-ABL* gene amplification and the development of alternative pathways of disease progression that are not targeted by imatinib, such as the SRC family kinases (SFKs).

Another important clinical barrier to the use of imatinib is drug toxicity leading to the discontinuation of treatment, also referred to as intolerance.[4] After 7 years, 5% of patients in the IRIS trial discontinued therapy because of adverse events.[23] In a retrospective review of a managed care database (n = 216), imatinib therapy was suspended because of drug toxicity in 29% of patients, most often because of anemia (11%) or thrombocytopenia (11%).[24] Furthermore, among patients in that analysis who suspended therapy, 26% had to discontinue treatment with imatinib permanently. Intolerance to imatinib occurs more frequently in advanced stages of CML, which is likely to be the result at least in part of the heightened morbidity in late-stage disease.[25–27] A further consideration is that patients with advanced-stage CML tend to receive higher doses of imatinib than patients with CML in CP —the approved doses for CML in AP/BP and CML in CP are 600 mg daily and 400 mg daily, respectively.[14] In the retro spective database review discussed above, the percentages of patients requiring a dose reduction who had starting doses of at least 400 mg daily, 600 mg daily, or 800 mg daily were 21%, 59%, and 67%, respectively.[24]

Imatinib dose escalation (600–800 mg daily) is a second-line therapeutic strategy for patients with CML after failure on standard-dose, first-line imatinib therapy.[4] The rationale for using second-line, high-dose imatinib therapy is supported by the results from a phase 1 dose-seeking trial (n ¼ 83) that revealed a direct association between higher doses of imatinib and observed responses.[11] Several studies of high-dose imatinib in patients with CML and failure on standard-dose, front-line imatinib have reported cytogenetic responses in 30% to 50% of patients. However, those investigations also indicated that the best responses attained were lost in 40% to 50% of patients and that treatment-related outcomes were not consistent among all patients.[4,28–31] Recent data have suggested that this option should be reserved for patients with minimal disease burden, ie, cytogenetic recurrence rather than hematologic recurrence.[4] High-dose imatinib is associated with increased myelosuppression.[4]

Current NCCN guidelines and ELN recommendations indicate that alternative TKI therapies should be considered for patients who develop resistance or intolerance to imatinib.[18,19] Approved second-line TKIs include dasatinib (Sprycel; Bristol-Myers Squibb Company, Princeton, NJ)[32] and nilotinib (Tasigna; Novartis Pharmaceuticals Corporation).[33] In the current review, we evaluated these TKIs and provide guidance to clinicians for the therapeutic selection of a second-line TKI.

DASATINIB

Dasatinib is a potent BCR-ABL TKI with 325-fold greater in vitro selectivity for unmutated BCR-ABL than imatinib.[34,35] In addition to blocking BCR-ABL kinase activity, dasatinib inhibits a distinct spectrum of oncogenic kinases, including SFKs, c-Kit, platelet-derived growth factor-receptor (PDGFR), and ephrin-A receptor.[36] Moreover, unlike imatinib, which only binds to the inactive conformation of the ABL kinase domain, dasatinib binds to both the active and inactive conformations.[34–37] Dasatinib is active in vitro against all imatinib-resistant BCR-ABL imatinib-resistant tency than imatinib, dasatinib also may have activity in patients with imatinib resistance caused by BCR-ABL overexpression.[37] The

effect of dasatinib on alternative signaling pathways (eg, SFKs) may enable it to overcome BCR-ABL-independent resistance to imatinib.[37]

Dasatinib was approved by the FDA in 2006 for the treatment of imatinib-refractory CML in all phases and Ph-positive acute lymphoblastic leukemia (ALL).[32] Approval was granted based on the efficacy and safety outcomes demonstrated in the open-label, phase 2 v-src sarcoma (SRC)/ABL Tyrosine Kinase Inhibition Activity: Research Trials of Dasatinib [START]) studies in patients with CML or Ph-positive ALL that was resistant or intolerant to first-line imatinib therapy.[31,38–41]

Significant efficacy in patients with CML in CP who received second-line dasatinib 70 mg twice daily was evident in the START-C phase 2 study (n = 387).[42] The 2-year CCyR rate was 53%, and the median time to achieve these responses was 5.5 months. In addition, confirming response durability, 90% of CCyRs were maintained after 24 months. The 2-year PFS and OS rates were 80% and 94%, respectively.[43]

The START-R study compared responses to dasatinib 70 mg twice daily with responses to high-dose imatinib (400 mg twice daily) in 150 patients with CML in CP who had already experienced resistance to imatinib 400 to 600 mg daily.[31] At the 2-year follow-up, dasatinib demonstrated significantly higher rates of CCyR (44% vs 18%; $P = .0025$). Rates of complete hematologic response (CHR), MCyR, major molecular response (MMR), and PFS also favored dasatinib ($P < .05$). This superiority over high-dose imatinib also was durable. After 18 months, the MCyR was maintained in 90% of dasatinib-responding patients compared with 74% of imatinib-responding patients. In addition, the START-A, START-B, and START-L studies demonstrated that dasatinib 70 mg twice daily possessed a high level of clinical activity and generally was well tolerated in patients who had CML in AP, CML in BP, and Ph-positive ALL, respectively.[38,39,41,44]

On the basis of data from the START trials, the recommended starting dose for dasatinib initially was 70 mg twice daily for all indications. However, based on additional evidence from dose-optimization studies, the dasatinib prescribing information recently was updated to include new recommended starting doses of 100 mg once daily for patients with CML in CP and 140 mg once daily for patients with CML in AP, CML in BP, or Ph-positive ALL.[45–49] The CP CML dose-optimization study (n = 670) evaluated 4 different dosing schedules: 100 mg once daily, 50 mg twice daily, 140 mg once daily, and 70 mg twice daily[45] Marked and comparable hematologic and cytogenetic response rates were observed across the 4 treatment groups. In particular, dasatinib 100 mg once daily was as effective as the previously recommended dose of 70 mg twice daily. After a minimum follow-up of 6 months, the 100-mg once-daily and 70-mg twice-daily regimens yielded similar rates for MCyR (59% vs 55%, respectively) and CCyR (41% vs 45%, respectively). The durability of cytogenetic responses to the 100-mg once-daily regimen was confirmed over long-term follow-up: CCyR rates were 39%, 45%, and 50% at 6 months, 12 months, and 24 months, respectively.[46] At 36 months, the PFS and OS rates were 73% and 87%, respectively. In total, 36 patients experienced progression events while receiving dasatinib 100 mg once daily (n = 164). The majority of patients (86%) who progressed while receiving dasatinib remained in CP at 36 months.[50]

Also noteworthy was the finding that the 100-mg once-daily regimen was tolerated better than the 70-mg twice-daily regimen, with significantly lower rates of pleural effusion (all grades, 7% vs 16%; $P = .024$) and grade 3 or 4 thrombocytopenia (22% vs 37%; $P = .004$). The most common hematologic adverse events of any grade reported with dasatinib 100 mg once daily included anemia (89%), neutropenia (63%), and thrombocytopenia (60%). Common nonhematologic adverse events were headache (30%), diarrhea (23%), fluid retention (21%), and fatigue (20%). Fewer patients who were receiving dasatinib 100 mg once daily experienced dose interruption (51% vs 68%), reduction (30% vs 55%), or discontinuation (16% vs 23%) after a 6-month minimum follow-up.

The other phase 3, dose-optimization study compared a 140-mg once-daily dose of dasatinib with the 70-mg twice-daily dose in patients (n = 611) with CML in AP, CML in BP, or Ph-positive ALL who were resistant or intolerant to imatinib.[47–49] Among patients with CML in AP who were randomized to receive once-daily or twice-daily treatment, the 2-year rates were comparable for major hematologic response (66% vs 68%, respectively) and MCyR (39% vs 43%, respectively).[47] The once-daily and twice-daily regimens also were similar with regard to the 24-month PFS (51% vs 55%, respectively) and OS (63% vs 72, respectively). The once-daily regimen was associated with an improved safety profile compared with the twice-daily regimen. Significantly fewer patients who were receiving once-daily treatment experienced a pleural effusion (all grades: 20% vs 39%; $P < .001$). Likewise, in subsets of patients with CML in BP and Ph-positive ALL who were followed for 2 years in this phase 3 study, both schedules were associated with similar efficacy, but significantly fewer adverse events and treatment interruptions were noted with once-daily treatment.[48,49]

Because accumulating evidence attests to the high activity of dasatinib as second-line therapy for CML, research efforts are beginning to focus on reasons for dasatinib resistance. It is believed that progression of CML involves additional cytogenetic abnormalities (eg, trisomy 8, trisomy 19, and isochromosome 17q).[9] Clonal evolution confers imatinib resistance[51,52] and is an independent poor prognostic factor for survival[51] and a significant predictor for hematologic recurrence and inferior PFS.[52] Little is known about the impact of clonal evolution on second-line treatment with dasatinib. A small study (n = 71) of patients with any phase of CML who were receiving second-line dasatinib demonstrated that cytogenetic responses were compromised among the 31% of patients with clonal evolution (n = 22) after a median follow-up of 9 months.[53] MCyR was attained in 14% of patients with clonal evolution, compared with 42% of those without clonal evolution. These findings underscore the potential importance of clonal evolution in CML resistance and point to the need for additional larger studies. The relation between BCR-ABL mutations and dasatinib resistance is explored below.

The recommended treatment option for patients who fail second-line TKI treatment is allogeneic hematopoietic SCT.[19] Currently, treatment with nilotinib after dasatinib failure is not recommended; however, it is the subject of an ongoing phase 2 study.[54] After a median follow-up of 12 months in patients who had previously failed on both imatinib and dasatinib, nilotinib elicited an MCyR rate of 43% in 39 patients with CML in CP and a confirmed hematologic response rate of 29% in 17 evaluable patients with CML in AP. Estimated OS

rates are 86% at 18 months in patients with CML in CP and 80% at 12 months in patients with CML in AP.

NILOTINIB

Another TKI that can be used in CML after failure with first-line imatinib is nilotinib.[4] Approved by the FDA in 2007 for treating patients with Ph-positive CML in CP and AP (but not CML in BP or Ph-positive ALL) who are resistant or intolerant to imatinib,[33] nilotinib is an imatinib analog with 30 times more potency than imatinib at in vitro BCR-ABL inhibition.[13,34] Other kinase targets for nilotinib include PDGFR and c-Kit receptors.[4] Nilotinib is active against all imatinib-resistant BCR-ABL mutations except T315I.[55] Like imatinib, nilotinib binds an inactive conformation of ABL but may overcome most BCR-ABL mutants through its greater potency.[37] In a 24-month update, nilotinib produced a CCyR in 44% of patients with CML in CP who had failed on imatinib.[56] The rate of PFS in this population was 64%.[57]

The recommended dose for nilotinib is 400 mg administered twice daily approximately 12 hours apart.[33] Food should not be ingested for at least 2 hours before and for at least 1 hour after the dose is taken, because food increases the bioavailability of nilotinib.

The clinical activity of nilotinib in the setting of imatinib-resistant or imatinib-intolerant CML was demonstrated in 2 pivotal, open-label, single-arm, phase 2 studies, including 1 study in patients with CML in CP and another study in patients with CML in AP.[56,58] The CP CML trial involved 321 patients who were imatinib resistant (30%) or imatinib intolerant (70%) and had a minimum follow-up of 19 months.[56] An MCyR was achieved in 59% of patients at a median of 2.8 months, and a CCyR was achieved by 44% of patients at a median of 3.3 months. Responses were durable, with 78% and 83% of patients maintaining MCyRs and CCyRs, respectively, at 24 months. The OS rate was 88% at 24 months. At 2-year follow-up, treatment had been discontinued in 59% of participants because of disease progression (27%), drug-related adverse events (15%), or other reasons (17%).[59] The AP CML trial involved 137 patients who were imatinib resistant (80%) or imatinib intolerant (20%) and had a minimum follow-up of 11 months.[58] A CHR was achieved in 31% of patients at a median of 1 month after the initiation of therapy, and an MCyR was achieved in 32% of patients at a median of 2.8 months. A CCyR was achieved in 20% of patients, and >70% of those patients remained in CCyR at 24 months. The OS rate was 67% at 24 months.

Among patients with CML in CP, nilotinib was well tolerated and had a favorable risk-benefit profile.[56] The most common grade 3 or 4 laboratory abnormalities were elevated lipase (17%), hypophosphatemia (16%), hyperglycemia (12%), and elevated total bilirubin (8%). Grade 3 or 4 nonhematologic adverse events were infrequent, with rash, headache, and diarrhea occurring in 2% of patients. The most common grade 3 or 4 hematologic adverse events were neutropenia (31%), thrombocytopenia (31%), and anemia (10%). Pleural or pericardial effusions (all grades) occurred in 2% of patients, and grade 3 or 4 pleural or pericardial effusions were rare (<1%).

Currently, treatment with an additional TKI is not recommended after failure on second-line TKI therapy, as stated above. However, a study in 23 patients (19 of whom were in advanced stages of CML) who failed on both imatinib and nilotinib demonstrated that dasatinib induced a CHR rate of 43% and a cytogenetic response rate of 30%, including 2 CCyRs and 1 PCyR.[60] Another case study has indicated that dasatinib may overcome BCR-ABL mutation-independent resistance in patients who are resistant to both imatinib and nilotinib.[61]

IMPLICATIONS FOR THE CLINIC

TKIs have shifted the treatment paradigm for CML, offering patients effective and well tolerated therapeutic options. Standard-dose imatinib (400 mg daily) is the only currently approved front-line TKI therapy for patients with CML. Most patients respond to first-line imatinib therapy, but resistance and intolerance occur in some patients. For patients who have treatment failure with imatinib, second-line options should be explored. Dose escalation of imatinib in the second line is not an appropriate approach for patients who experience drug toxicity, as mentioned above. NCCN guidelines indicate that dasatinib and nilotinib should be considered in patients with resistance or intolerance to imatinib.[18] Both are potent and specific BCR-ABL TKIs, yet each has distinct pharmacologic properties that should be considered when planning second-line therapy.

Substantial long-term efficacy data are now available for TKIs administered as second-line therapy for CML (Table 1), although prospective randomized trials comparing dasatinib with nilotinib have not been performed. Dasatinib and nilotinib are highly effective and have been approved for the treatment of patients with CML in CP or AP who are resistant or intolerant to imatinib therapy, inducing rapid and durable hematologic and cytogenetic responses. Dasatinib also is effective and has been approved for the treatment of patients with CML in BP and patients with Ph-positive ALL who are resistant or intolerant to imatinib therapy. Twenty-four-month data from separate trials revealed MCyR rates for dasatinib and nilotinib at the currently recommended doses of 63% and 59%, respectively, among patients with CML in CP[56,62] and 39% and 32%, respectively, among patients with CML in AP.[31,58] The 24-month OS rates for dasatinib and nilotinib were 91% and 88%, respectively, among patients with CML in CP[56,62] and 63% and 67%, respectively, among patients with CML in AP.[31,58]

Making cross-trial comparisons of response and outcome between dasatinib and nilotinib can be problematic and difficult to interpret. Study design characteristics, such as inclusion criteria and definitions of response and progression, vary between the clinical trials that have evaluated these agents. For instance, in a multicenter phase 2 study of dasatinib, a CHR was determined based on patients who attained or maintained a CHR regardless of prior response with imatinib.[40] However, in multicenter studies of nilotinib, a CHR was assessed only in patients who did not have a CHR at baseline.[63] Furthermore, the phase 3 dose-optimization trial of dasatinib also enrolled patients who had a suboptimal response to imatinib, whereas large trials of nilotinib did not include that population.[45] These differences also extend to the criteria for intolerance, such that large studies with dasatinib considered patients with grade 3 or 4 toxicity as imatinib intolerant regardless of their cytogenetic response. Nilotinib-

specific trials excluded patients who had a prior MCyR to imatinib in the intolerant population. Finally, the definition of progression also has differed between multicenter dasatinib-specific and nilotinib-specific trials. Progression in dasatinib studies traditionally has included the loss of hematologic or cytogenetic response, increasing white blood cell count, a sizeable increase in Ph-positive meta-phases, transition to advanced phases of CML, or death. Progression in nilotinib studies is defined only by transition to advanced phases of CML or death. Because the progression reported in dasatinib-focused studies is defined more strictly, resulting in a lower PFS rate, many patients who are classified as progressing with dasatinib would not fall under that category in nilotinib studies. This suggests that the survival outcomes with these 2 agents should monitored as important endpoints.

In addition to efficacy outcomes, mutational data should be considered when selecting TKI therapy.[4] The *BCR-ABL* genotype can be used to guide treatment decisions, because it is a prognostic factor for disease progression.[64–67] Patients with the threnoine-to-alanine/isoleucine mutation at codon 315 (T315A/I), the phenyalanine-to-isoleucine/leucine mutation at codon 317 (F317I/L), and the valine-to-leucine mutation at codon 299 (V299L) do not appear to respond consistently to therapy with dasatinib[4,65,66]; whereas patients with the phenylalanine-to-cysteine/valine substitution at codon 359 (F359C/V) do benefit from dasatinib.[4,40] In an analysis of 1043 patients who underwent mutational assessment in phase 2/3 studies of CML in CP, 14 patients had baseline F317L mutations, and only 1 patient had a baseline V299L mutation.[68] Those investigators observed that patients with F317L mutations achieved a high CHR rate (93%), but cytogenetic response rates (MCyR, 14%; CCyR, 7%) were lower than in patients without these mutations. It is noteworthy that, among patients who received dasatinib, high response rates were obtained with the common imatinib-resistant mutations in Y253, E255, and E359 residues.

Nilotinib resistance is associated with mutations in the T315, Y253, and E255 residues.[4] Indeed, recently, it was demonstrated that the presence of E255K/V, Y253H, or F359C/V mutations at baseline were independent predictors of worsened PFS in patients with CML in CP.[69] Therefore, dasatinib therapy may be more appropriate for patients with these common mutations, whereas nilotinib may be better suited for those with F317L mutations.[4] Although both dasatinib and nilotinib are ineffective against T315I BCR-ABL,[4] this mutation is more likely to affect patients in the advanced phases of CML.[22,70] Patients with T315I may achieve favorable outcomes with therapies other than the available second-line TKIs, eg, AP24534, omacetaxine, and others.[4]

Safety and tolerability also are important considerations in choosing a TKI, especially among patients with certain comorbidities. Serious cases of pleural effusion can occur with dasatinib therapy but are more common in advanced phases (grade 3 or 4: 2% with CML in CP and 7% with CML in AP).[31,62] Because both imatinib and nilotinib rarely are associated with pleural effusion (≤1% incidence),[14,33] these agents may be more appropriate therapies for patients with pulmonary disease or with a high susceptibility to pleural effusions.[4] At currently recommended doses, grade 3 or 4 myelosuppression may be similar for nilotinib and dasatinib. In patients with CML in CP, grade 3 or 4 neutropenia and thrombocytopenia were observed in 35% and 23% of patients who were receiving dasatinib, respectively, after a minimum 2 years of follow-up.[62] For nilotinib, grade 3 or 4 neutropenia and

thrombocytopenia were induced in 31% of patients who were receiving nilotinib after a minimum follow-up of 19 months.[57] Serious bleeding events (eg, intracranial and gastrointestinal bleeding) have been reported with the use of TKIs, and clinicians as well as patients should be vigilant for warning signs.[14,32,33] With dasatinib, bleeding has been noted particularly among patients with CML in AP/BP and low platelet counts.[71] QT interval prolongation has occurred on rare occasions with nilotinib and dasatinib.[32,33] Therefore, it is recommended that all patients who are receiving nilotinib and dasatinib should be screened for risk factors of QT prolongation (eg, hypokalemia, hypomagnesemia, congenital long QT syndrome, and concurrent medications that can lead to QT prolongation).[18] There is a strict predose and postdose fasting requirement with nilotinib, because food substantially alters the drug's bioavailability, which may increase the risk for QT interval prolongation.[33] Nilotinib is the only TKI that carries a black-box warning.[4]

In conclusion, TKIs have revolutionized the treatment of CML, rapidly becoming standards of care. Imatinib, as the first approved TKI for front-line treatment of patients with CML, has changed the natural history of CML. However, resistance and intolerance are challenges faced by some patients who receive imatinib, and there is a need for alternative treatments. Current guidelines support the use of dasatinib or nilotinib as second-line therapy among patients with CML who fail on first-line imatinib therapy. The efficacy and safety of dasatinib and nilotinib as second-line therapy have been confirmed by substantial long-term outcome and response durability data, and it is clear that these agents exhibit unique pharmacologic profiles and response patterns relative to different patient characteristics, such as disease stage and BCR-ABL mutation status. To optimize therapeutic benefit, clinicians should select a second-line TKI while keeping these considerations in mind.

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Table 1

Response and Survival Rates for Patients Receiving Second-Line Tyrosine Kinase Inhibitor Therapy for Chronic Myeloid Leukemia

	24-Month Response Rate, %	
Response to Agent	**Chronic Phase**	**Accelerated Phase**
Dasatinib, 70 mg twice daily	n=387 (Mauro 2008[42])	n=174 (Rea 2008[44])
CHR[a]	91	50
MCyR	62	40
CCyR	53	33
PFS[b]	80	46
OS	94	72
Nilotinib	n=321 (Kantarjian 2009[56,57])	n=137 (Hochhaus 2009[58])
CHR[c]	94	31
MCyR	59	32
CCyR	44	20
PFS	64	NR
OS	88	67
High-dose imatinib, 400 mg twice daily	n=49 (Kantarjian 2009[31])	–
CHR	82	NA
MCyR	33	NA
CCyR	18	NA

CHR indicates complete hematologic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; PFS, progression-free survival; OS, overall survival; NR, not reported; NA, not applicable.

[a] Including patients who had a CHR at baseline.

[b] Including loss of hematologic or cytogenetic response, increasing white blood count, increase in Philadelphia chromosome-positive metaphases, transition to advanced phases of CML, or death.

[c] Excluding patients who had CHR at baseline.