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First-Line Use of Second-Generation Tyrosine Kinase Inhibitors in Patients With Chronic Myeloid Leukemia

INTRODUCTION

Chronic myeloid leukemia (CML), a hematopoietic stem cell disease, is characterized by a reciprocal chromosomal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome (Ph+).[1] The bcr-abl oncogene, a fusion protein with tyrosine kinase activity, results from this translocation, and leads to the development of CML.[1,2] Treatment of patients with Ph+ CML in chronic phase with the tyrosine kinase inhibitor (TKI) class of oral agents—imatinib, nilotinib, and dasatinib, which selectively bind to the bcr-abl kinase domain—generally leads to complete cytogenetic remission with minimal adverse events.[3-6]

Imatinib, a first-generation TKI, has been the standard of care for patients with Ph+ CML for the past decade.[3,7] However, the development of resistance mechanisms to imatinib, in addition to poorly tolerated adverse events in some patients, has resulted in a new unmet need.[3] Results of 2 randomized phase III studies of 2 more potent second-generation TKIs, nilotinib[5] and dasatinib,[6] recently demonstrated significantly better response compared with imatinib in the treatment of newly diagnosed Ph+ CML patients. Notable results included higher rates of complete cytogenetic remission, faster time to remission, and reduced

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rates of disease progression.[3,5,6] Based on these studies, the United States Food and Drug Administration (FDA) granted a new indication for nilotinib in newly diagnosed patients in June 2010 and a priority review of data supporting the use of dasatinib in newly diagnosed patients with Ph+ CML in chronic phase.[8,9] The first-line indication for nilotinib, and potentially that of dasatinib, presents the opportunity for a new standard of care in the treatment of Ph+ CML.[5,9]

Oncology nurses play a pivotal role in monitoring patients with Ph+ CML, from those who are newly diagnosed to others who may have been receiving TKI treatment for years. Indications, dosing, and characteristics of second-generation oral TKIs, including potential drug-drug interactions and adverse events, and how best to manage them, are explored in this article. Two case studies of representative patients are also presented to provide an understanding of treatment considerations for Ph+ CML.

DISEASE-STATE OVERVIEW

If left untreated, CML usually progresses through 3 clinically recognized phases: chronic, accelerated, and blast.[1,10] Although patients most commonly progress through all 3 stages, 20% to 25% progress directly from the chronic phase to the blast phase.[10] The time course for disease progression is also quite varied.[10]

Pathophysiology

The cytogenetic hallmark of CML is the Ph+, created by a reciprocal translocation between chromosomes 9 and 22 (t[9;22][q34;q11]).[10] The conjugation of the breakpoint cluster region (bcr) gene on chromosome 22 and the Abelson (abl) kinase gene on chromosome 9 creates the bcr-abl oncogene. This codes for a deregulated tyrosine kinase, leading to uncontrolled cell proliferation, reduced apoptosis, and malignant expansion of pluripotent stem cells in the bone marrow.[10] Oral TKIs—imatinib, nilotinib, and dasatinib—selectively inhibit bcr-abl through different binding mechanisms.[3]

Epidemiology and Risk Factors

There are few known risk factors for CML. In most cases, no cause can be found, and CML cannot be prevented by lifestyle changes. The only known environmental risk factor is exposure to high-dose radiation (ie, an atomic bomb blast or nuclear reactor accident).[11]

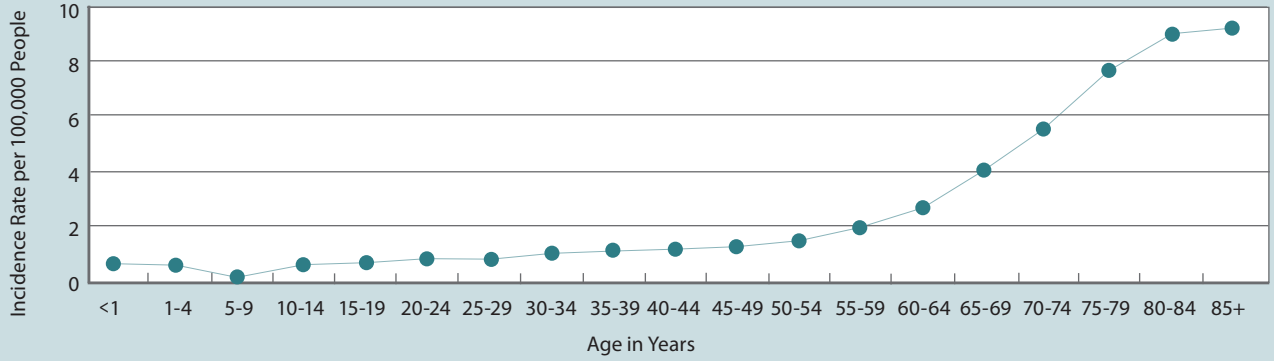
Incidence and prevalence: Approximately 11% of all adult leukemias are CML.[12] The risk of CML increases with age **(Figure 1)**[13] and occurs to a slightly greater degree in males than in females.[11] Median age of onset of CML is 67 years;[1] however, CML can occur in any age group.[13]

Morbidity/mortality: An estimated 5050 cases of CML were diagnosed in the US in 2009 and 470 patients died of their disease.[12] In 2009, approximately 22,473 people in the US were living with CML.[14] Patients with chronic-phase CML that remains untreated will eventually progress to more aggressive phases within 3 to 5 years.[1,15]

DIAGNOSIS

Approximately 40% of patients with CML may be asymptomatic at the time of diagnosis; in these patients, an abnormal blood count may be the only finding that suggests a diagnosis of CML.[15] Signs and symptoms of CML develop gradually and may include fatigue, anorexia, or weight loss.[15] Approximately 90% of patients are diagnosed during

FIGURE 1. Age-Specific Incidence Rates for Chronic Myeloid Leukemia, 2002-2006



Although median age of onset of CML is 67 years, the disease can occur in any age group. Incidence increases with age.

Source: Horner 2010.[13]

the indolent chronic phase.[10] The most common finding on physical examination at diagnosis is splenomegaly, which is present in up to one-half of patients.[15] The National Comprehensive Cancer Network (NCCN) Guidelines recommend that initial evaluation of adult patients with chronic-phase CML include[1]:

- History and physical examination, including spleen size palpitation
- Complete blood count with differential, including platelet counts
- Chemistry profile
- Bone marrow aspirate and biopsy

Bone marrow aspirate and biopsy are preferred in the initial evaluation to confirm CML diagnosis.

Bone marrow aspirate and biopsy are preferred in the initial evaluation to confirm CML diagnosis because of the ability to detect chromosomal abnormalities that may not be found in peripheral blood.[1] Bone marrow also provides a basis for a morphology review.[1] However, cytogenetic testing using fluorescence in situ hybridization (FISH) or quantitative reverse-transcriptase polymerase chain reaction (QRT-PCR) assay may be used to confirm a CML diagnosis in the event bone marrow cannot be attained.[1] QRT-PCR, which measures bcr-abl transcript levels, has shown strong correlations between peripheral blood and bone marrow results, demonstrating it as an accurate means of confirming diagnosis.[1]

TREATMENT AND RESPONSE

In the treatment of Ph+ CML, it is important to evaluate the response to therapy, particularly cytogenetic response, hematologic response, and molecular response. Response to therapy may vary with each patient.[1] The NCCN criteria for determining cytogenetic, hematologic, and molecular response when assessing patients with Ph+ CML are summarized in **Table 1**.

While CML may be cured by invasive procedures, (ie, bone marrow transplantation), significant progress has been made, both in understanding the disease and in the development of multiple, non-invasive treatment options.[1] Among the available treatment options are the class of oral TKIs.

Imatinib, one of the success stories of molecular medicine, was the first therapy designed to target the bcr-abl oncogene that causes CML.[10] Previously, treatment options for patients with Ph+ CML in chronic phase included interferon-alpha plus daily low-dose cytarabine.[16] After its approval in 2001 for the advanced stages of CML and in 2002 for newly diagnosed Ph+ CML,[17] imatinib clinically demonstrated its efficacy in a large number of patients[10] by inducing hematologic and cytogenetic remissions in all phases of CML.[2,7]

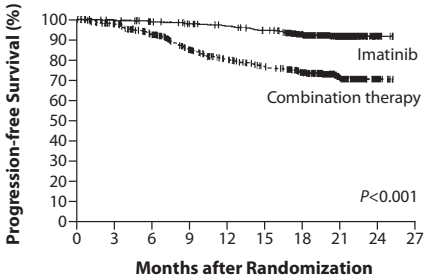
Evidence of imatinib's potential was noted in the International Randomized Study of Interferon and STI571 [imatinib] (IRIS) clinical trial, published in 2003.[4] IRIS evaluated imatinib for cytogenetic response rates and the development of accelerated-phase or blast-phase CML

TABLE 1. Criteria for Assessing Cytogenetic, Hematologic, and Molecular Response

Partial hematologic response	• Same as complete hematologic response, except for: –Presence of immature cells –Platelet count <50% of the pretreatment count, but >450 x 10^9/L –Persistent splenomegaly, but <50% of the pretreatment extent
Complete hematologic response	• Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood • No signs and symptoms of disease with disappearance of palpable splenomegaly
Cytogenetic response[a]	• Complete: no Ph+ metaphases • Major: 0%-35% Ph+ metaphases (complete + partial) • Partial: 1%-35% Ph+ metaphases • Minor: >35% Ph+ metaphases
Molecular response	• Complete molecular response: bcr-abl mRNA undetectable by RT-PCR • Major molecular response ≥3-$\log_{10}$ reduction of bcr-abl mRNA

[a]A minimum of 20 metaphases should be examined.
mRNA = messenger RNA. RT-PCR = reverse-transcriptase polymerase chain reaction.
Source: NCCN.[1]

FIGURE 2. Kaplan–Meier Estimates of Time to Major Cytogenetic Response Rates



No. of Events								
Imatinib	2	7	12	18	29	41	42	42
Combination therapy	12	38	73	94	108	119	125	125
No. at Risk								
Imatinib	543	530	518	505	487	392	162	7
Combination therapy	498	442	376	334	302	255	99	7

Progression was defined by any of the following events, whichever came first: death, accelerated-phase or blast-crisis CML, loss of response, or an increasing white cell count. The *P* value is for the difference between treatment groups within each risk group.
Source: O'Brien 2003.[4]

versus the existing standard of care, interferon-alpha plus daily low-dose cytarabine.[4]

Overall study results showed that imatinib was significantly superior to the standard, combination therapy with interferon-alpha plus daily low-dose cytarabine in the results of major cytogenetic response rates **(Figure 2)**, complete cytogenetic response, and progression-free survival at 18 months ($P<0.001$).[4]

Ultimately, imatinib became the standard frontline therapy for patients with Ph+ CML in chronic phase. Long-term outcomes with imatinib have documented an 8-year event-free survival rate of 81% and an estimated overall survival of 85%.[18] However, >30% of patients treated with imatinib do not achieve a complete cytogenetic response at 12 months.[7]

Suboptimal responses with imatinib may be the result of resistant mechanisms that develop over time. Patients with CML who become resistant to imatinib may have either primary or secondary resistance.[1,19] Primary resistance is defined by lack of efficacy at treatment onset, as identified by the NCCN as a failure to reach complete hematologic remission to imatinib within 3 to 6 months; failure to achieve any cytogenetic response at 6 months; major cytogenetic response at 12 months; or complete cytogenetic response at 18 months.[1,19] After an initial response to treatment with imatinib, a patient may develop secondary, or acquired, resistance (relapse). Acquired resistance is defined as a loss of previously achieved hematologic or cytogenetic response or progression of CML while on imatinib treatment.[19] An example of acquired resistance was clearly seen in the IRIS trial, where, after 5 years, 17% of those who initially responded to treatment with imatinib subsequently relapsed and 7% progressed to accelerated-phase or blast-phase CML.[7]

The incidence of primary and acquired resistance also increases with the progression of CML.[20] Among patients with advanced disease (accelerated phase or blast phase) versus those in chronic phase, response rates are lower. For that reason, patients who are receiving treatment with imatinib should be monitored continuously, to improve detection of secondary resistance as early as possible.[7,21]

Resistance mechanisms have also been uncovered over recent years and may explain why some patients have only a partial response when treated with TKIs. The most common mechanisms of imatinib resistance are bcr-abl kinase domain mutations. At least 30 point mutations that code for different single amino-acid substitutions in this domain have been detected in CML patients who are imatinib resistant.[19] The 3 main regions of the domain where mutations have been detected are: 1) the amino-terminal ATP phosphate-binding (P-loop); 2) the catalytic domain and intervening sequences containing amino acids that contact imatinib; and 3) the carboxyl-terminal activation loop, which is involved in the control of catalytic activity.[19]

It was hypothesized that treatment with more potent TKIs—nilotinib and dasatinib—would decrease disease progression.

Studies have shown that P-loop mutations are associated with a less favorable prognosis compared to non–P-loop mutations.[22] While some mutations may be managed by interrupting or stopping imatinib therapy (ie, P-loop mutations E255K and Y253F), or by using combination therapy, others require the use of alternative therapies; an example of this is seen with imatinib-resistant mutations F359C/V and F317L, which are sensitive to dasatinib and nilotinib, respectively.[1,21] Currently, there is one mutation that may be resistant to all available agents, as is the case with the T315I mutation, which confers resistance to imatinib, nilotinib, and dasatinib.[19] Research is ongoing to determine whether this mutation can be overcome with alternative drug treatment.[3]

TABLE 2. Reported Adverse Events with Imatinib

Adverse Events Reported in Newly Diagnosed CML Clinical Trial (≥10% of Imatinib–Treated Patients)[b]	All Grades Imatinib N=551 (%)
Fluid retention	61.7
Superficial edema	59.9
Other fluid retention events[c]	6.9
Muscle cramps	49.2
Diarrhea	45.4
Rash and related terms	40.1
Vomiting	22.5

[b]All adverse events occurring in ≥10% of imatinib-treated patients are listed regardless of suspected relationship to treatment.
[c]Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.
Source: GLEEVEC [package insert].[17]

In patients treated with imatinib, nurses may also detect adverse events such as edema, nausea and vomiting, rash, fatigue, and cytopenia. The most common adverse events reported by newly diagnosed patients taking imatinib were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea, and rash; the frequency of adverse events in newly diagnosed CML patients are noted in **Table 2**.[17]

Management of these adverse events includes treatment of symptoms or discontinuation of therapy until symptoms resolve, followed by treatment at the same dose (for grade 1 adverse events); discontinuation of therapy until symptoms resolve, followed by treatment at a reduced dose (for grade 2 or 3 adverse events); or drug discontinuation (grade 4 adverse events).[21] When resistance to imatinib is detected—whether primary or acquired—treatment should be changed promptly to ensure the best opportunity for a positive treatment outcome.[21]

Emerging resistance patterns, as seen in >20% of patients treated with imatinib in the IRIS study,[7] and adverse events have led clinicians to consider alternative therapies for managing their Ph+ CML patients. It was hypothesized that treatment with more potent TKIs—such as the second-generation agents nilotinib and dasatinib, which are less vulnerable to resistance-conferring mutations in the bcr-abl kinase domain and may have an improved tolerability profile—would decrease disease progression in CML.[6,23] Initial results of recently completed clinical studies suggest that use of more potent TKIs first-line will begin to change the treatment paradigm for this disease.[5,8]

Nilotinib, originally approved as a second-line agent for CML patients who developed resistance or intolerance to imatinib, is now approved as a first-line agent for newly diagnosed CML patients.[8] Although the study on which the recent indication approval is ongoing, further data will be required to determine long-term survival and safety outcomes.[7] Dasatinib, currently being studied for first-line approval, has been granted an accelerated review by the FDA.[9]

SECOND-GENERATION TYROSINE KINASE INHIBITORS

Treatment considerations depend on disease stage, adverse-event profile of the drug selected, and the drug's relative effectiveness against bcr-abl mutations.[1] Although nilotinib and dasatinib are both second-generation TKIs and are more potent than imatinib, differences exist between these agents.

Nilotinib

Approved by the FDA in 2007, nilotinib was first indicated for the treatment of chronic-phase and accelerated-phase Ph+ CML in adult patients who are intolerant or resistant to prior therapy, including imatinib.[8] Based on the results of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study, which is discussed in more detail throughout this article, nilotinib gained a second indication in 2010 for use as a first-line treatment option in patients with newly diagnosed Ph+ CML in the chronic phase.[8] Efficacy of nilotinib is based on major molecular response and cytogenetic response rates, and ongoing, long-term studies will help determine long-term outcomes.[8]

In newly diagnosed Ph+ CML patients, the recommended dose of nilotinib is 300 mg orally twice daily.[8] Conversely, a dose of 400 mg orally twice daily is recommended for patients who are resistant or intolerant to other treatments including imatinib.[8] Each dose of nilotinib should be taken on an empty stomach, either 2 hours before food or at least 1 hour after food, at 12-hour intervals.[8]

Dose adjustments and reductions for nilotinib may be made based on the occurrence of QTc prolongation (>480 msec), neutropenia, and thrombocytopenia unrelated to the underlying condition, and for nonhematologic laboratory abnormalities, including grade 3/4 elevations in serum lipase, amylase, bilirubin, and hepatic transaminases.[8] Nilotinib is primarily metabolized by the liver; therefore, patients with hepatic impairment should be closely monitored since elevated serum levels of nilotinib may induce or enhance

QT interval changes.[8] In newly diagnosed Ph+ CML patients with mild, moderate, or severe hepatic impairment, initial recommended dosing of nilotinib is 200 mg twice daily followed by an increase to 300 mg twice daily, if tolerated.[8] The dosing regimen for second-line use of nilotinib in patients with mild or moderate hepatic impairment is 300 mg twice daily, with a subsequent dose increase to 400 mg twice daily, if tolerated. It is recommended that patients with severe hepatic impairment receive 200 mg twice daily initially, followed by sequential dose escalations to 300 mg twice daily and, subsequently, 400 mg twice daily, if tolerated.[8]

It is important to monitor for drug interactions in patients treated with nilotinib. Concomitant use of nilotinib with medication and food products that inhibit or induce cytochrome P450 (CYP) enzymes, particularly CYP3A4, should be avoided.[8] Nilotinib is metabolized primarily by CYP3A4; strong CYP3A4 inhibitors (ie, ketoconazole, clarithromycin, grapefruit juice) may significantly increase nilotinib exposure, thus increasing the likelihood of drug-related adverse events.[8] Concomitant use of CYP3A4 inducers (ie, carbamazepine, rifampin, dexamethasone) may lead to significant decreases in nilotinib serum levels, rendering the treatment ineffective.[8]

Antiarrhythmics, such as amiodarone and procainamide, as well as other medications that may cause QT prolongation, should be avoided with nilotinib. QT prolongation may also occur if nilotinib is inappropriately administered with food or with strong CYP3A4 inhibitors, due to the significant elevations in serum levels that may occur as a result.[8] The effect leading to an increased risk of QT prolongation may be enhanced if hypokalemia and hypomagnesemia are also present; to minimize this risk, hypokalemia and hypomagnesemia should always be corrected prior to administration of nilotinib.[8] If simultaneous use of these treatment options and nilotinib is necessary, and alternatives are not available, close monitoring becomes a crucial component of patient management and care.[8]

The clinical trial [ENESTnd] supporting first-line use of nilotinib showed a favorable safety profile.

Nilotinib has decreased solubility at higher pH levels; as a result, an important drug interaction to note involves agents that alter gastric pH levels, such as H_2-receptor antagonists (H_2RAs), antacids, and proton-pump inhibitors (PPIs). Concomitant use of these agents and nilotinib may decrease the bioavailability, and ultimately the efficacy, of nilotinib.[8] It is recommended to separate the dose of H_2RAs and antacids by several hours from that of nilotinib.[8] Since gastric pH may be affected for an extended period with certain agents, as seen with PPIs, separating the dose of nilotinib from the PPI may not be sufficient to eliminate the drug interaction.[8] Therefore, if an alternative is not available, caution is recommended when a PPI is used with nilotinib.[8]

The clinical trial supporting first-line use of nilotinib showed a favorable safety profile. The most commonly reported (>10%) nonhematologic adverse events with nilotinib included rash, pruritus, headache, nausea, fatigue, and myalgia.[8] Less commonly observed adverse events (>5% and ≤10%) are upper abdominal pain, alopecia, constipation, diarrhea, dry skin, muscle spasms, arthralgia, peripheral edema, and asthenia, all of which were mild to moderate in severity and did not require the dose of nilotinib to be reduced.[8] Pleural and pericardial effusions have also been documented in 1% of patients.[8] Increases in QT intervals >60 msec from baseline were also reported in 0.4% of patients in the clinical trial using nilotinib as a frontline option; however, no patient had an absolute QTcF >500 msec.[8] The most common hematologic adverse events (all grades) included thrombocytopenia (17%), neutropenia (15%), and anemia (7%).[8] The incidence of grade 3/4 myelosuppression was less common: neutropenia (12%), thrombocytopenia (10%), and anemia (4%).[8]

Dasatinib

Dasatinib is also a potent second-generation TKI that gained its original FDA approval in 2006.[24] Currently, dasatinib holds an indication for the treatment of chronic, accelerated, myeloid, or lymphoid blast-phase CML in adults who are resistant or intolerant to prior therapy, including imatinib; and for the treatment of Ph+ acute lymphoblastic leukemia in adults who are resistant or intolerant to prior therapy.[24] However, a supplemental NDA for a new indication as a treatment for newly diagnosed adults with CML in chronic phase was submitted to the FDA and is currently undergoing a priority review. Results of the review are expected in late 2010.[9]

Dasatinib can be taken either in the morning or in the evening, without regard to meals.[24] For the treatment of chronic-phase CML, the recommended starting dose for dasatinib is 100 mg orally once daily; for CML in the

accelerated phase or blast phase (myeloid or lymphoid), 140 mg of dasatinib orally once daily is recommended as the starting dose.[24]

Dasatinib is also a substrate of the CYP450 enzyme system, particularly CYP3A4. Coadministration of strong inhibitors of CYP3A4 (ie, ketoconazole) and dasatinib should be avoided due to an increase in dasatinib plasma concentrations that may result.[24] If an alternative is unavailable, a dose reduction of dasatinib and close monitoring for toxic effects are recommended.[24] Conversely, using a strong inducer of CYP3A4 with dasatinib may reduce dasatinib plasma concentrations; as a result, a dose increase of dasatinib may be necessary, and patients should be monitored for toxicity.[24]

Agents that alter gastric pH, such as antacids, H_2RAs, and PPIs also interact with dasatinib; the solubility of dasatinib is pH dependent, and simultaneous use of these agents can decrease dasatinib plasma concentrations.[24]

With an understanding of differences and similarities of TKIs, oncology nurses can play a pivotal role in addressing patient concerns.

As a result, H_2RAs and PPIs should be avoided; on the other hand, if acid suppression is needed, antacids may be administered either 2 hours before or 2 hours after the dasatinib dose.[24]

Dasatinib may also affect plasma concentrations of other therapeutic agents. Drugs that have a narrow therapeutic index and are substrates of CYP3A4 (ie, cyclosporine, simvastatin) should be used with caution due to potential plasma concentration elevations.[24]

The use of dasatinib is associated with the development of severe (grade 3 or 4) thrombocytopenia, neutropenia, and anemia; these adverse events were more commonly reported in patients with more advanced stages of CML.[24] Overall, grade 3 or 4 myelosuppression was less likely to be reported with the 100 mg once-daily dose.[24] Dosing of dasatinib may be adjusted if neutropenia or thrombocytopenia develops.[24]

Throughout clinical studies with dasatinib, severe bleeding, primarily associated with severe thrombocytopenia, has also been reported.[24] Approximately 1% and 4% of patients experienced severe central nervous system hemorrhages or severe gastrointestinal hemorrhages, respectively.[24] As a result, caution should be used when administering dasatinib to patients taking anticoagulants or other medications that alter platelet function.[24]

Fluid retention has also been reported throughout clinical studies with dasatinib; in 10% of patients, fluid retention was severe and reports included pleural effusions (7%) and pericardial (1%) effusions.[24] It is recommended that patients who develop signs of pleural effusion, such as dyspnea or dry cough, be evaluated with a chest X-ray and, if results are positive, managed with supportive care measures (ie, diuretics, steroids).[24]

Caution should be used when dasatinib is administered to patients at risk of developing QT prolongation. High-risk patients include those with hypokalemia, hypomagnesemia, those who have previously developed prolonged QT intervals, or patients taking medications that may lead to QT prolongation (ie, antiarrhythmics, high-dose anthracycline therapy). In clinical studies with dasatinib, QT prolongation was noted in <1% (14/2182) of patients; QT intervals >500msec had been reported in 1% of patients (21/2182).[24]

It is important to note that certain adverse events may be more frequent with one agent compared to another, as had been reported in clinical studies. With an understanding of differences and similarities of second-generation TKIs, oncology nurses can play a pivotal role in addressing patient concerns as well as be in a better position to set patient expectations.

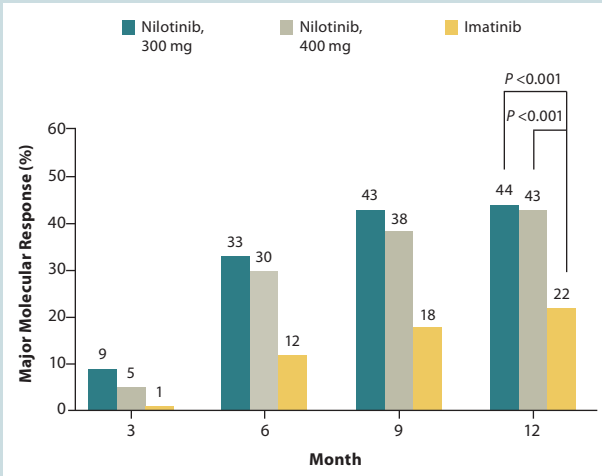
CLINICAL STUDIES

ENESTnd

Clinical evidence supporting the first-line use of nilotinib in newly diagnosed Ph+ CML patients has been recognized in a phase III, open-label, multicenter study, Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd).[5] The objective of the ENESTnd study was to compare safety and efficacy of nilotinib with imatinib in patients newly diagnosed with Ph+ CML in chronic phase.[5]

To determine the efficacy of nilotinib in this patient population, the rate of major molecular response at 12 months was used as the study's primary end point.[5] The molecular response was assessed for bcr-abl by real-time QRT-PCR assay at baseline, monthly for the first 3 months, then every 3 months.[5] The primary end point was established by a bcr-abl transcript level ≤0.1% in peripheral blood on QRT-PCR assay on the International Scale, which corresponds to a reduction of 3-$\log_{10}$ copies or more in bcr-abl transcripts.[5] The rate of complete cytogenetic response by 12 months was the main secondary end point

FIGURE 3. Major Molecular Response Rates with Nilotinib



The results of the intention-to-treat population were calculated by means of the Cochran–Mantel–Haenszel test, stratified according to the Sokal risk group, after the last patient had completed 12 cycles of therapy (with a 28-day duration for each cycle). Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.

Source: Saglio 2010.[5]

of the study; disease progression to the accelerated phase or blast phase was also evaluated.[5]

Eligible patients included those diagnosed with Ph+ CML in the chronic phase within the previous 6 months; no previous treatment for CML, with the exception of anagrelide or hydroxyurea, was allowed. The diagnosis needed to be confirmed by a cytogenetic analysis; a diagnosis by using the FISH procedure was not allowed. An Eastern Cooperative Oncology Group (ECOG) performance status score of at least 2 and adequate organ function were also required.[5]

Study patients were randomized in a 1:1:1 ratio to receive one of the following[5]:

- Nilotinib 300 mg twice daily
- Nilotinib 400 mg twice daily
- Imatinib 400 mg once daily

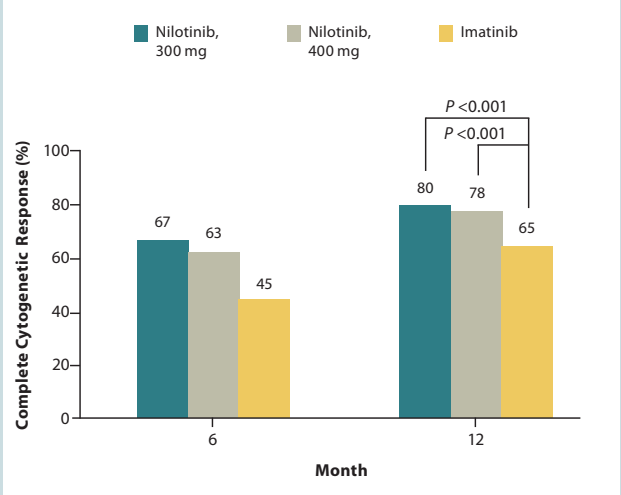
Patients were allowed to discontinue therapy for different reasons, including evidence of treatment failure (ie, disease progression) or intolerable side effects. Dose escalation of imatinib to 400 mg twice daily was permitted in patients showing a suboptimal response or treatment failure; no dose escalations were allowed for patients receiving nilotinib.[5]

A total of 846 patients were randomized to receive either nilotinib twice daily or imatinib once daily: 282 and 281 patients were assigned to receive nilotinib 300 mg and 400 mg, respectively; and 283 patients were assigned to receive imatinib 400 mg.[5] The median duration of treatment was approximately 14 months.[5] At the time of data cutoff, 84% and 82% of patients were still receiving nilotinib 300 mg and 400 mg, respectively, compared with 79% of patients who received imatinib. In the imatinib group, 45 patients required a dose escalation to 800 mg.[5] At 12 months, 44% and 43% of patients receiving nilotinib 300 mg and 400 mg twice daily, respectively, achieved significantly higher rates of major molecular response compared to 22% of those receiving imatinib ($P<0.001$) **(Figure 3)**.[5]

As noted in Figure 3, the major molecular response rates were also higher in both nilotinib groups, when compared to the imatinib group, at 3, 6, and 9 months.[5] Additionally, the bcr-abl transcript level was ≤0.0032% (approximately 4.5-$\log_{10}$ reduction)on the International Scale in 13% and 12% of patients receiving nilotinib 300 mg and 400 mg, respectively, compared to 4% of patients receiving imatinib.[5]

Complete cytogenetic response rates were also significantly different between imatinib and nilotinib; results showed 80% and 78% of patients in the nilotinib 300 mg and 400 mg groups, respectively, had a complete cytogenetic response, compared to 65% of patients receiving imatinib ($P<0.001$ for both comparisons) **(Figure 4)**.[5] Disease progression to the accelerated phase or blast phase occurred in 11 (4%) patients receiving imatinib, 2 (<1%) patients receiving nilotinib 300 mg, and 1 (<1%) patient

FIGURE 4. Complete Cytogenetic Response Rates with Nilotinib



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Source: Saglio 2010.[5]

CASE 1

USE OF NILOTINIB IN A TREATMENT-NAÏVE PATIENT

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PATIENT PRESENTATION

During a routine physical examination, JD, a white, 39-year-old realtor in good health, was found to have an elevated white blood cell (WBC) count of 11,000/µL. His primary care physician believed JD had an infection and treated him with a short course of antibiotics. Follow-up laboratory tests a few months later showed WBC had increased to 16,000/µL. Despite completion of a second course of antibiotics, his WBC did not improve.

PATIENT HISTORY AND DIAGNOSIS

JD underwent further diagnostic testing, including repeated blood tests, fluorescence in situ hybridization (FISH) analysis, and cytogenetic testing.

Laboratory Test Results

- WBC: 16,500/µL
- Hemoglobin: 14.5 g/dL
- Platelets: 180,000/µL
- Basophils: 6%
- Myelocytes: 4%
- Neutrophils: 52%
- Promyelocytes: 2%
- **Bone marrow biopsy:** myeloid hyperplasia with immature forms; 6% blasts
- **FISH analysis:** bcr-abl gene rearrangements observed in 97% of the 200 interphase nuclei
- **Cytogenetic testing:** abnormal karyotype with a reciprocal t(9;22) translocation observed in all 20 evaluated metaphase cells

Assessment: The elevated WBC, in addition to the presence of bcr-abl-positive cells and a t(9;22) translocation, confirm a diagnosis of chronic-phase Ph+ CML.

TREATMENT

- Nilotinib 300 mg twice daily without food, either 2 hours before a meal or 1 hour after a meal, (ie, before breakfast and after dinner)
- Regularly complete and assess cardiac rhythm using an electrocardiogram (ECG) prior to initiating therapy and changes in dose; monitor blood count, liver function, amylase, and lipase levels

FOLLOW-UP

- After 4 weeks of initiating therapy, blood tests showed JD developed grade 3 thrombocytopenia (30,000/µL). Nilotinib was held for 2 weeks, but further blood tests showed his platelet count remained significantly low. Nilotinib was resumed at a reduced dose of 400 mg once daily. ECG and blood tests were repeated 7 days later after dose change
- Six weeks later, blood tests showed platelets increased to 160,000/µL; subsequently, the nilotinib dose was titrated back to 300 mg twice daily
- After the titration another ECG, completed 1 week later, showed an increase in QT interval to 480 msec; nilotinib was held for 2 weeks while JD was evaluated
- Upon questioning JD about recent diet and medication changes, he mentioned his sister recently gave him a bag of grapefruit from her trip to the farmer's market the previous week, which he had been consuming on a regular basis. After suspending the grapefruit, another ECG showed normalized QT intervals, and therapy with nilotinib was resumed at a dose of 300 mg twice daily. JD was monitored regularly with follow-up ECGs
- After a total of 12 weeks on nilotinib and regular blood cell count monitoring, JD achieved a complete hematologic response; repeat CBC showed a normal WBC of 4500/µL, hemoglobin of 14.5 g/dL, and platelets of 175,000/µL

DISCUSSION

Thrombocytopenia is a hematologic adverse event that can occur with nilotinib; neutropenia may occur as well.[8] Therefore, regular monitoring of blood chemistries should be part of every patient's treatment regimen. Among the primary nonhematological adverse events that can occur with nilotinib, ECG changes (eg, QT prolongation) may occur.[8] For patients newly prescribed nilotinib, an ECG should be conducted before the patient takes the first dose, 7 days after initiating treatment with nilotinib, periodically during treatment, and after any dose changes. Laboratory tests should be conducted every other week as indicated, or more frequently, based on clinical judgment.[8] Adverse events may be dose related and can be managed by dropping or stopping the dose, then resuming treatment when the problems have abated. As demonstrated in this case, dietary and medical changes (ie, new medications) may also impact therapy and must be considered when evaluating patients who present with new adverse events.

Source: TASIGNA [package insert].[8]

receiving nilotinib 400 mg (P=0.01; P=0.004, respectively).[5] None of the patients who achieved a major molecular response showed evidence of progression to the accelerated phase or blast phase; however, 3 patients receiving imatinib did have disease progression despite achieving a complete cytogenetic response.[5]

Throughout the study, both nilotinib and imatinib had favorable safety and adverse event profiles; overall, grade 3 or 4 nonhematological events were uncommon. Nausea, diarrhea, vomiting, muscle spasms, and edema occurred at higher rates in the imatinib group than in the nilotinib groups; rash, headache, pruritus, and alopecia were reported at higher rates in the nilotinib groups than in the imatinib group.[5] With regard to hematological events, grade 3 or 4 neutropenia (20%) and anemia (5%) were more common in the imatinib group, whereas thrombocytopenia (10% [300 mg]; 12% [400 mg]) occurred more frequently in both nilotinib groups; all new grade 3 or 4 hematological abnormalities occurred within the first 2 months for all groups.[5] None of the patients among the 3 study groups showed evidence of QT prolongation >500 msec or a change in the mean left ventricular ejection fraction from baseline.[5]

Approximately 5% and 9% of patients receiving nilotinib 300 mg and 400 mg, respectively, discontinued the study due to adverse events, compared to 7% of those receiving imatinib.[5]

None of the patients among the [nilotinib or imatinib] study groups showed evidence of QT prolongation >500 msec.

Overall, the results of this study demonstrated that nilotinib was superior to imatinib with tolerable adverse events; both major molecular response and complete cytogenetic response, the primary and secondary end points, respectively, were significantly higher with nilotinib compared to imatinib. These therapeutic milestones are important, particularly in newly diagnosed patients, as they are predictors of the treatment prognosis; in this study, they correlated with the significantly lower disease progression or transformation rates seen in the nilotinib groups, when compared to the imatinib groups, thereby confirming that twice-daily nilotinib, at both 300 mg and 400 mg doses, is superior to imatinib in newly diagnosed patients with Ph+ CML.[5] Additional follow-up, comprised of monitoring of patients in this study for up to 24 months, is ongoing and will provide more information about potential long-term advantages, disadvantages, response durability, and adverse events associated with nilotinib therapy.[5]

DASISION

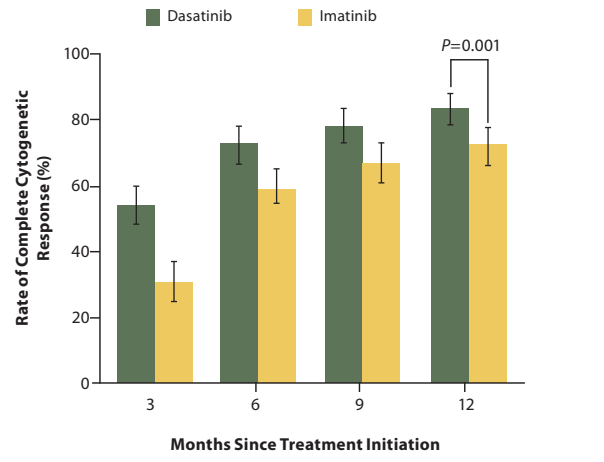
Dasatinib has also been evaluated in newly diagnosed, chronic-phase CML patients in the Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION) study. DASISION, an open-label, multinational, randomized phase III trial, compared the efficacy and safety of dasatinib to that of imatinib when used in newly diagnosed CML patients.[6] The primary objective was to determine whether patients who received dasatinib had a higher rate of confirmed complete cytogenetic response after 12 months of treatment, compared to imatinib.[6]

A complete cytogenetic response was defined as a complete response documented on 2 consecutive assessments at least 28 days apart; bone marrow samples were used to assess cytogenetic response within 6 weeks after randomization and every 3 months thereafter. Patients who had a complete cytogenetic response by 12 months and an assessment confirming the complete response thereafter were considered to have a complete cytogenetic response at the 12-month time frame.[6]

Secondary study end points included a major molecular response at any time, the time to a confirmed complete cytogenetic response, and the time to a major molecular response.[6] Major molecular response rates were determined using QRT-PCR to measure bcr-abl transcripts; a major molecular response was defined as a bcr-abl transcript level ≤0.1%, which corresponds to a reduction of 3-$\log_{10}$ copies or more in bcr-abl transcripts on the International Scale.[6]

For participation in the study, patients were required to have Ph+ CML in chronic-phase diagnosed by bone marrow cytogenetic studies within 3 months of study entry.[6] Previous treatment for CML, with the exception of anagrelide or hydroxyurea, was not allowed, and patients were required to have an ECOG performance status of 0 to 2.[6] Patients were randomized to receive either dasatinib 100 mg once daily (with or without food) or imatinib 400 mg once daily (with food) in a 1:1 ratio; dose escalations, reductions, and interruptions were allowed for both treatment groups, based on predetermined criteria.[6] Treated patients were evaluated for all adverse events, including pleural effusion, throughout the entire study.[6]

FIGURE 5. Complete Cytogenetic Response Rates with Dasatinib



A total of 10 patients (5 in each group), in whom the assessment of complete cytogenetic response was based on bone marrow samples containing fewer than 20 cells in metaphase per sample, were categorized as not having a response. I bars indicate 95% confidence intervals.

Source: Kantarjian 2010.[6]

Of the patients randomized, 258 patients in both treatment groups received their respective study drug; the median duration of the treatment was 14 months for the dasatinib group and 14.3 months for the imatinib group.[6]

By 12 months of treatment, 77% of patients receiving dasatinib, compared to 66% of those taking imatinib, had a confirmed complete cytogenetic response; the difference between both groups was significant ($P=0.007$).[6] Complete cytogenetic response observed in at least 1 assessment by 12 months of treatment was also higher, respectively, with dasatinib compared to imatinib (83% vs 72%, $P=0.001$).[6] The rates of a complete cytogenetic response were achieved at earlier time frames with dasatinib than with imatinib, as noted in **Figure 5** (HR 1.5, $P<0.0001$).[6]

Additionally, patients who received dasatinib, compared to those who received imatinib, had a significantly higher rate of major molecular response at any time (52% vs 34%, $P<0.0001$) and by the end of the 12-month study period (46% vs 28%, $P<0.0001$).[6] The time to major molecular response was significantly shorter with dasatinib compared to imatinib (HR 2.0, $P<0.0001$) as denoted in **Figure 6**.[6]

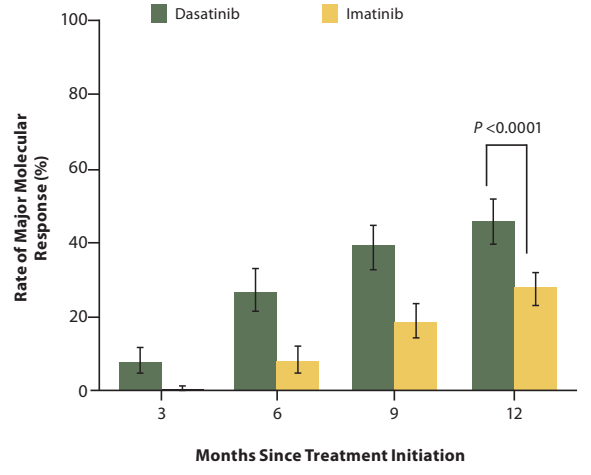
Disease progression occurred in 1.9% of patients receiving dasatinib (5/259), compared to 3.5% of patients receiving imatinib (9/260); all patients' disease progressed to the blastic phase.[6] Progression-free survival was similar between both treatment groups.[6]

Adverse events in the dasatinib and imatinib groups were primarily grade 1 or 2. Nonhematologic adverse events occurring in at least 10% of patients included nausea, vomiting, muscle inflammation, rash, and fluid retention; these adverse events occurred more frequently in the imatinib group. All grades of fluid retention, as well as superficial edema, were more frequently reported in the imatinib group, compared to the dasatinib group (42% vs 19% and 36% vs 9%, respectively).[6] Grade 1 or 2 pleural effusion events were reported by 10% (26 patients) receiving dasatinib; pleural effusion was not reported in patients receiving imatinib.[6] Hypophosphatemia (grade 3 or 4) also occurred at higher frequencies with imatinib (21%) compared to dasatinib (4%).[6]

Grade 3 or 4 neutropenia occurred in 21% and 20% of patients in the dasatinib group and imatinib group, respectively; thrombocytopenia occurred in 19% of patients receiving dasatinib and in 10% of patients receiving imatinib.[6] QTc intervals between 450 msec and 500 msec occurred in 2% and 4% of patients in the dasatinib group and imatinib group, respectively; one patient in each treatment group had a QTc interval >500 msec.[6]

Discontinuation due to adverse events occurred in 5% and 4% of patients receiving dasatinib and imatinib, respectively.[6] Four deaths occurred in the dasatinib group, whereas 1 death occurred in the imatinib group; 1 death in each group was attributed to the study treatment and was the result of a myocardial infarction.[6]

FIGURE 6. Major Molecular Response Rates with Dasatinib



A total of 8 patients (5 in the dasatinib group and 3 in the imatinib group) with atypical transcripts at baseline were categorized as not having a response. I bars indicate 95% confidence intervals.

Source: Kantarjian 2010.[6]

CASE 2

SWITCHING A PATIENT TO DASATINIB WHEN IMATINIB THERAPY FAILS

Phyllis McKiernan, RN, MSN, OCN, APN

PATIENT PRESENTATION

MP is a 54-year-old white production manager who complained of a 2-month history of increasing fatigue and upper left quadrant discomfort.

PATIENT HISTORY AND DIAGNOSIS

Physical

- Spleen was palpable 2 cm below the left costal margin

Laboratory Test Results

- WBC: 189,000/µL
- Hemoglobin: 8.4 g/dL
- Platelets: 125,000/µL
- **Bone marrow biopsy:** hypercellular marrow with leukemic blast cells
- **Cytogenetic testing:** positive translocation between chromosomes 9 and 22 in 20 of 20 evaluated metaphases

Assessment: Confirmed diagnosis of Ph+ CML in chronic phase

TREATMENT

- Treatment initiated with imatinib 400 mg/day
- Blood counts monitored weekly until improvement was noted

FOLLOW-UP

- After 3 months of therapy with imatinib, blood tests showed
  - WBC: 9700/µL
  - Hemoglobin: 12.5 g/dL
  - Platelets: 165,000/µL, indicating a complete hematologic response
  - MP complained of ankle edema that improved with a decrease in his dietary sodium intake
- After 6 months of treatment, MP's blood counts remained within normal limits, and his spleen was no longer palpable. Bone marrow examination showed the Ph+ chromosome in 4/20 metaphases by standard cytogenic testing, indicating a major partial response (defined as 1% to 34% Ph+ metaphases).[1]
- At 9 months of treatment, a complete hematologic response was maintained. Molecular testing showed a 1-$\log_{10}$ reduction in the bcr-abl transcripts
- At 12 months, despite a normal blood count, bone marrow testing showed persistent Ph+ chromosomes in 4 of 20 metaphases, indicating no further response. Molecular testing revealed no significant change in bcr-abl fusion transcripts

CHANGE IN THERAPY

- A mutation analysis testing for the emergence of bcr-abl mutations that might indicate a resistance to TKIs was negative. Due to MP's suboptimal response to imatinib, he was switched to dasatinib 100 mg/day after ECG and electrolytes were monitored

FOLLOW-UP

- After 6 months of treatment with dasatinib, MP's bone marrow showed a normal male karyotype with no Ph+ cells detected by standard cytogenetics or by fluorescense in situ hybridization
- Molecular testing revealed a major molecular response (>3-$\log_{10}$ reduction)[1]
- Adverse events included transient anemia, a moderate skin rash treated successfully with topical corticosteroids, and grade 2 pleural effusion. To manage the pleural effusion, dasatinib was discontinued for 2 weeks and diuretics were administered. Dasatinib was restarted when pleural effusion resolved; MP was monitored for recurrence
- After 9 months of treatment with dasatinib, molecular testing revealed no bcr-abl transcripts, indicating a complete molecular response

DISCUSSION

In general, second-generation TKIs are well tolerated, but adverse events can occur. One of the adverse events observed with dasatinib is pleural effusion.[24] Periodic physical examinations should include assessment of breath sounds to detect pleural effusion. If this occurs, dose modification, therapy interruption, or a switch in therapy to nilotinib or imatinib, may be required, depending on severity. Cytopenias, including transient anemias, are evidenced by a drop in blood counts and must be monitored regularly with blood chemistry panels. Routine skin exams well also help check for rash. QT intervals should also be monitored regularly during treatment.[24] The goal is to maintain the patient on continuous drug therapy, with minimal interruptions.

Strategies for handling adverse events such as headache and musculoskeletal pain can be discussed with the patient to ensure that those strategies are congruent with the patient's lifestyle.

It may be appropriate to switch the patient to another TKI if treatment is frequently discontinued. It is also important for nurses to be aware that when a patient is switched from one TKI to another, it can be a frightening event for the patient. Patients should be assured that other options are available to achieve treatment milestones and that to achieve the optimal response, multiple treatment trials may be needed.

Sources: NCCN[1]; SPRYCEL [package insert].[24]

Overall, the results of this study demonstrated that dasatinib is effective in newly diagnosed Ph+ CML chronic-phase patients. Both complete cytogenetic response and major molecular response rates were significantly higher in patients who received dasatinib, which can potentially indicate a lower risk for long-term disease progression. The adverse events reported in this trial also demonstrated that the safety profile for dasatinib is acceptable, compared to that of imatinib.[6] Long-term results from this ongoing study will better evaluate the potential benefits and risks of using dasatinib in treatment-naïve patients, as well as determine the potential of improved progression-free survival.[6]

DISCUSSION: ENESTnd and DASISION

When considering the potential impact both trials may have on treatment selection, the relevance and strength of the study end points are of critical importance. Evaluation of the major molecular response rate, based on the reductions in bcr-abl transcript levels, is a recommended measure in the evaluation of residual disease CML patients. In 2005, an expert committee concluded that residual disease should be expressed on an international scale based on a standard baseline value (established in the IRIS trial) and a standardized major molecular response value of 0.1% (equivalent to a 3-$\log_{10}$ reduction from the standard baseline).[25] Past studies have demonstrated that major molecular response rates based on bcr-abl transcript reductions serve as better long-term prognosticators for disease progression.[26] Moreover, a major molecular response can potentially lead to higher rates of progression-free survival and event-free survival.[25] A cytogenetic evaluation using Ph+ metaphases may not be as sensitive in the detection of minimal residual disease.[26]

Oncology nurses address patient concerns, using a step-care approach, and can help set patient expectations.

With regard to adverse events, both nilotinib and dasatinib are well tolerated. Based on QT prolongation warnings that apply to both nilotinib and dasatinib, ENESTnd excluded all patients with impaired cardiac function[5]; similarly, DASISION excluded patients with uncontrolled or serious cardiovascular disease, including patients with corrected QT intervals.[6] Despite these exclusions, there were patients in DASISION who experienced QT prolongation >500 msec as an adverse event; in addition, one documented death in each treatment group was related to a cardiac event.[6] This occurrence not only demonstrated that cardiac patients necessitate additional monitoring if treated with dasatinib or imatinib, but also that QT prolongation is not limited to certain agents within the TKI class—it is a warning that applies to this pharmacological class as a whole.

Ultimately, both nilotinib and dasatinib have demonstrated efficacy in the treatment of patients with Ph+ CML in chronic phase.[5,6] The key differentiating factor that will determine which agent is better for a given patient is the safety profile, tolerability, and the management of adverse events, when encountered.

CONCLUSION

As discussed throughout this article, there has been an evolution in the way CML patients are managed today compared to strategies used a decade ago.

Oncology nurses continue to play a key role in the management and care of patients with Ph+ CML. As the skilled oncology nurse is aware, despite the similarities and differences apparent in agents within the same class, monitoring, documenting, and evaluating their effect in patients are essential to understanding the subtleties of each treatment regimen and to ensure the best possible patient outcome. Oncology nurses closely monitor resistance patterns and drug selection with an eye to therapeutic milestones; they are in an optimal position to recognize the severity of adverse events and suggest changes in therapy. More importantly, oncology nurses address patient concerns, using a step-care approach, and help set patient expectations; this is greatly due to the impact of research and the role of the oncology nurse in helping determine the potential long-term benefits or disadvantages of second-generation TKIs. More options now exist with the 3 available treatments that can help improve patient outcomes. The impact oncology nurses have in therapy selection cannot be underestimated.

Only continued patient follow-up and vigilant monitoring of treatment-related response and toxicity will help ensure the most effective patient care in CML as well as help provide data on durability of responses, emergence of treatment resistance, and long-term safety of current agents and those yet to come.

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ONLINE RESOURCES FOR HEALTHCARE PROVIDERS AND PATIENTS

A wealth of information is available on the Internet on chronic myeloid leukemia (CML), both for healthcare providers and patients. Programs and organizations also exist online to assist qualified patients in paying for their medications. Here is a sampling:

American Cancer Society
What is chronic myeloid leukemia? How is CML treated by phase? What is new in CML research? The answers to these and many other questions patients may ask about CML and cancer in general can be found on this Web site, which also includes information on wellness programs, treatment decision tools, and advice for caregivers.
1-800-227-2345
http://www.cancer.org

Destination Access (dasatinib)
Copay assistance for dasatinib, with the relevant forms and documents, is available on this Web site. A Patient Support Kit includes a welcome card, patient brochure, daily journal, and copay brochure and card. A Sprycel Support Advisor can be contacted by phone to help answer questions about the program.
1-800-861-0048
http://www.destinationaccess.com

GLEEVEC® (imatinib)
Disease-state information on CML and financial assistance information for patients are available on this Web site. For healthcare professionals, key details from the International Randomized Study of Interferons and STI571 (IRIS) trial, which compared imatinib to interferon, are presented. In addition, addressing adverse events and the importance of adhering to imatinib therapy are discussed.
1-866-972-8313
http://www.gleevec.com

Leukemia & Lymphoma Society
The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to funding blood cancer research, education, and patient services. For patients, the LLS Web site offers disease-state information on CML, news of new treatments and clinical trials, emotional and financial support, free materials, discussion boards, and a call center where information specialists can help patients with the challenges of their diagnosis and assistance in communicating with their healthcare teams. For healthcare providers, LLS-sponsored conferences, meetings, Webcasts, and teleconferences are among the offerings.
1-800-955-4572
http://www.leukemia-lymphoma.org

National Cancer Institute
Both patients and healthcare providers will find comprehensive information on CML on this Web site, including treatments; clinical trials; statistics related to CML incidence, mortality, and survival; information about coping with cancer; research literature on CML; and more.
1-800-422-6237
http://www.cancer.gov/cancertopics/types/leukemia

Novartis Patient Assistance Foundation
The Novartis Patient Assistance Foundation provides assistance to patients experiencing financial hardship who have no third party insurance coverage for their medicines. An enrollment form and further information are available on this Web site.
1-800-277-2254
http://www.pharma.us.novartis.com/info/about-us/our-patient-caregiver-resources/paf-enrollment.jsp

Patient Assistance Now (nilotinib)
This Web site lets patients access programs that may help them pay for their Novartis medications. A Program Finder tool helps them determine their eligibility for a given program and assists healthcare providers with insurance verification, denials/appeals, and more.
1-800-245-5356
http://www.patientassistancenow.com/index.jsp?

SPRYCEL® (dasatinib)
For healthcare providers, this Web site provides 2-year data on imatinib-resistant patients with CML in chronic phase who were treated with dasatinib 100 mg once daily, including study design, survival data, durability and cytogenic response, subset population, safety, and more.
1-800-321-1335
http://www.sprycel.com

TASIGNA® (nilotinib)
For patients, disease-state and treatment information for CML, as well as reimbursement information for nilotinib, can be found on this Web site. For healthcare professionals, product information, nilotinib safety and tolerability, treatment of Philadelphia chromosome-positive CML, and a downloadable patient education brochure are available.
1-866-411-8274
http://www.us.tasigna.com

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