Clinical intolerance occurs when the toxicity of a medication outweighs its clinical benefit. Early recognition of clinical intolerance to BCR-ABL inhibitors used for chronic myeloid leukemia (CML) is important for maximizing patient benefit. In CML, most side effects associated with BCR-ABL inhibitor therapy are mild and easily managed, so recognizing, monitoring, and addressing serious side effects may ensure optimal outcome. However, a subset of patients will be intolerant to first-line imatinib. Patients who experience unresponsive grade 3 or any grade 4 nonhematologic side effects to imatinib may require discontinuation and switching to second-line therapies, such as dasatinib or nilotinib, after identification of intolerance. The most common side effects associated with dasatinib and nilotinib are hematologic and generally are reversible with dose adjustment. Pleural effusions are more common with dasatinib use and may be managed by dose interruption and reduction. Both drugs possess warnings regarding QT prolongation, but nilotinib carries a black box warning for QT prolongation and sudden death.

**At a Glance**

- Oncology nurses need to recognize, monitor, and manage serious BCR-ABL inhibitor-associated side effects to help ensure optimal patient outcomes.
- Educating patients about potential side effects is vital and patients should be advised not to delay reporting them.
- A change in treatment may be required for a small subset of patients who develop clinical intolerance to BCR-ABL inhibitor-associated side effects.

Chronic myeloid leukemia (CML) is a hematologic disorder accounting for 15%–20% of all adult leukemias (Ault, 2007). The disease course of CML is usually triphasic, most often initiating in a chronic phase (CP), which is asymptomatic in 40% of patients (Alvarez, Kantarjian, & Cortes, 2007). Patients may progress to an accelerated phase (AP) and ultimately to blast phase (BP). The disease is characterized by the presence of the Philadelphia chromosome (Ph), a reciprocal translocation between chromosomes 9 and 22. The resulting fusion protein from Ph, called BCR-ABL, functions as a constitutively active tyrosine kinase and is responsible for the pathophysiology of CML (D’Antonio, 2005). The treatments of choice for patients with CML are tyrosine kinase inhibitors that target BCR-ABL and mitigate its activity. BCR-ABL inhibitors currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of CML include imatinib, dasatinib, and nilotinib. All BCR-ABL inhibitors are associated with side effects that require early recognition, vigilance, and appropriate treatment to ensure optimum outcomes. Oncology nurses play an integral role in that process; however, even with the best patient care, therapy-related toxicity is unavoidable and may require adjustments or an alternative therapeutic strategy.

Clinical intolerance to one of the available BCR-ABL inhibitors occurs when the toxicity of the medication outweighs the clinical benefits.
benefit provided at the optimized dose. Potential toxicities are described in the prescribing information for each agent. Intolerance to those compounds is a challenge of CML treatment, and, in some cases, a change in treatment strategy may be necessary. In addition, toxicities may lower patient adherence to the regimen, affect treatment efficacy, and prevent patients from fully benefiting from therapy. Recognition of such intolerance is, therefore, a particularly vital component of the nurse’s role in patient care. This review summarizes the safety profiles, monitoring, counseling, and management guidelines for each FDA-approved BCR-ABL inhibitor.

**Imatinib**

**Safety Profile**

Imatinib currently is approved for first-line therapy of CML. Approved starting doses are 400 mg daily in patients with CML-CP, and 600 mg daily in those with CML-AP or -BP (Novartis Pharmaceuticals, 2009). Imatinib has a well-established safety profile and has been used as effective therapy for all phases of CML since 2001. In the pivotal phase III IRIS (International Randomized Study of Interferon versus STI571) study that led to FDA approval, hematologic side effects were observed in individuals receiving imatinib (O’Brien et al., 2003). Neutropenia, thrombocytopenia, and anemia (all grades) were identified in 61%, 57%, and 45% of patients, respectively. Grade 3–4 neutropenia, thrombocytopenia, and anemia were observed in 14%, 8%, and 3% of patients, respectively (Novartis Pharmaceuticals, 2009).

The most common nonhematologic side effects (incidence greater than 30%; all grades) associated with imatinib in this study were superficial edema (56%), nausea (44%), muscle cramps (38%), fatigue (36%), rash (34%), diarrhea (33%), and headache (31%) (O’Brien et al., 2003). The most common grade 3–4 side effects (incidence 2% or greater) were musculoskeletal pain, joint pain, abdominal pain, and rash. The risk of imatinib-associated grade 3–4 edema and severe fluid retention was low and reported in 1.5% and 1.3% of patients, respectively. However, the risk of edema is increased for patients older than age 65 and also is more frequently observed in the legs (Guilhot, 2004; Novartis Pharmaceuticals, 2009).

In addition to the more common nonhematologic side effects, imatinib has been associated with rare side effects (e.g., severe congestive heart failure, left ventricular dysfunction); monitoring patients for signs of side effects is crucial (Novartis Pharmaceuticals, 2009). In a survey of patients entered on imatinib clinical trials (median time from start of imatinib therapy was 162 days), 0.6% of patients experienced cardiac events attributable to imatinib (Atallah, Durand, Kantarjian, & Cortes, 2007; Kerkela et al., 2006). Patients also are at risk for severe hepatic toxicity (manifested by elevated liver enzyme levels) and severe hemorrhage (which occurs mostly in the advanced stages of CML), with an overall incidence of those grade 3–4 adverse events in 2%–5% of patients. Gastrointestinal tract perforations, hypothyroidism, cardiogenic shock, and bullous dermatologic reactions were rare (incidence 1% or less) in study participants (Novartis Pharmaceuticals, 2009). In clinical trials of patients with CML-AP or -BP, hepatotoxicity occurred in 5% and 6% of patients, respectively, and grade 3–4 hemorrhage occurred in 19% and 11% of patients, respectively. In such cases, the condition resolves after the imatinib dose is lowered or discontinued. Therefore, vigilant patient assessment and monitoring are essential for the recognition of early toxicity. Early intervention may reduce the need for dose adjustment or interruption and ensure optimal patient adherence at the prescribed dose. Effective management of adverse events by oncology nurses also can reduce the risk of a premature switch to alternate BCR-ABL inhibitors before medically necessary.

**Patient Counseling and Monitoring**

The importance of monitoring and educating patients about potential side effects cannot be overstated. Because most patients will experience some level of toxicity, knowledge that those toxicities are expected and may be managed may alleviate much fear in patients. Patients should be advised not to delay in reporting any side effects, particularly fever, dyspnea, melana, jaundice, sudden weight gain, and other symptoms of cardiac failure. A detailed history should include past medical history for cardiac disease or cardiac risk factors (Novartis Pharmaceuticals, 2009).

Each patient visit should include a comprehensive review of all medications, including over-the-counter supplements. Because imatinib is metabolized primarily by hepatic CYP3A4 enzymes, other compounds known to interact with those enzymes have the potential to alter the plasma concentrations of imatinib (Novartis Pharmaceuticals, 2009) (see Figure 1). In addition, grapefruit juice must be avoided (Novartis Pharmaceuticals, 2009). If a strong CYP3A4 inducer must be administered concomitantly with imatinib, the imatinib dosage should be increased by 50% or more and clinical response monitored closely (Novartis Pharmaceuticals, 2009). Acetaminophen-containing preparations and alcohol increase the risk of hepatic toxicity and should be avoided (Ault, 2007). Antiseizure medications such as phenytoin and carbamazepine should not be coadministered with imatinib. In addition, imatinib may affect the plasma concentrations of other drugs taken concomitantly (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010). In particular, patients who require anticoagulation should be given low-molecular-weight or standard heparin rather than warfarin (Novartis Pharmaceuticals, 2009).

Imatinib is recommended to be taken with a meal and a large glass of water to avoid gastrointestinal tract irritation (D’Antonio, 2005; Novartis Pharmaceuticals, 2009), and the patient must remain upright for at least 30 minutes after taking imatinib to avoid reflux (Ault, 2007). Women of childbearing potential should avoid pregnancy. Breastfeeding mothers should be instructed to discontinue breastfeeding (Novartis Pharmaceuticals, 2009).

**Management**

For hematologic side effects, growth factor support may be indicated (National Comprehensive Cancer Network [NCCN], 2010). Side effects may be controlled with a supportive treatment, such as diuretic, antidiarrheal, and antiemetic agents; topical steroids; and nonsteroidal anti-inflammatory drugs (Ault, Kaled, & Rios, 2003; D’Antonio, 2005; Guilhot, 2004; NCCN, 2010). However, grade 3–4 side effects may require a reduction in dosage or an interruption or cessation of treatment (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010) (see Table 1).
Patients with cardiovascular disease or who are at risk for cardiac failure should be monitored closely and treated accordingly (Novartis Pharmaceuticals, 2009) (see Table 2). Specific steps for muscle cramps include prescribing calcium supplements, quinine, and tonic water (Ault, 2007; D’Antonio, 2005; Novartis Pharmaceuticals, 2009, 2010). Salt reduction and diuretic agents may be helpful for periorbital edema. Skin rash may be treated with antihistamines, salves, coal tar preparations, and topical steroids (Ault, 2007; Guilhot, 2004).

Discontinuation

Imatinib discontinuation should be considered in the event of an unresponsive grade 3 nonhematologic side effect or any grade 4 nonhematologic side effect (NCCN, 2010; Novartis Pharmaceuticals, 2009). In pivotal clinical studies for dasatinib and nilotinib in patients with CML-CP, imatinib intolerance sufficient to require discontinuation was defined as the occurrence of any grade 4 hematologic side effect lasting longer than seven days or grade 3 or higher nonhematologic side effect (Hochhaus et al., 2007; Kantarjian et al., 2007). The key nilotinib study also defined imatinib intolerance as a grade 2 nonhematologic side effect lasting one month or longer or recurring more than three times despite optimal dose adjustment and supportive interventions (Kantarjian et al., 2007). The most common side effects leading to discontinuation of imatinib in the pivotal studies were rash, hepatotoxicity, arthralgias, gastrointestinal tract events, and edema (Hochhaus et al., 2007; Kantarjian et al., 2007).

BCR-ABL inhibitors available as therapeutic options following imatinib discontinuation include dasatinib and nilotinib. Dasatinib is approved by the FDA for treatment of patients with newly diagnosed Ph-positive CML-CP, as well as CML-CP, -AP, and -BP, and Ph-positive acute lymphocytic leukemia in patients who are intolerant of or resistant to prior therapy, including imatinib (Bristol-Myers Squibb, 2010). Nilotinib is approved for the treatment of patients with newly diagnosed Ph-positive CML-CP and CML-CP or -AP intolerant of or resistant to prior therapy, including imatinib (Novartis Pharmaceuticals, 2010).

Dasatinib

Safety Profile

Dasatinib currently is approved for the treatment of newly diagnosed Ph-positive CML-CP, and also for patients with CML-CP, -AP, or -BP that is resistant to or intolerant of prior therapy, including imatinib. The approved dosages are 100 mg once daily in CML-CP and 140 mg once daily in CML-AP and -BP, with or without food (Bristol-Myers Squibb, 2010). In general, most side effects of dasatinib therapy are hematologic, mild to moderate (grades 1–2) in severity, and resolve spontaneously or with appropriate supportive care. Minimal recurrence of side effects associated with imatinib intolerance (e.g., grade 3–4 liver function abnormalities or rash) has been noted (Cortes et al., 2007; Guilhot et al., 2007; Hochhaus et al., 2007). Lack of nonhematologic cross-tolerance with imatinib was later confirmed in a retrospective safety analysis (Khoury et al., 2008). Dasatinib is associated with high rates of treatment adherence and low rates of toxicity-related withdrawal (Cortes et al., 2007; Guilhot et al., 2007; Hochhaus et al., 2007). Rates of discontinuation from drug-related adverse events ranged from 9%-11% with dasatinib (Cortes et al., 2007; Hochhaus et al., 2007).

Dasatinib originally was approved by the FDA at a dose of 70 mg twice daily for all indications in the second-line setting. However, based on data from a phase III dose-optimization study, the dose for patients with CML-CP is now 100 mg once daily, preserving the same level of efficacy as before, but improving the safety profile (Shah et al., 2008, 2010). In that phase III study, the most common side effects were hematologic. After a minimum of two years of follow-up, in the 100 mg once daily arm, rates of grade 3–4 neutropenia, thrombocytopenia, and anemia were 35%, 25%, and 13%, respectively (Shah et al., 2010). With the previously approved 70 mg twice daily dose, rates of grade 3–4 neutropenia, thrombocytopenia, and anemia were 45%, 38%, and 18%, respectively. In the phase III front-line trial of dasatinib (100 mg once daily), after a minimum follow-up of 12 months, the incidence of grade 3–4 neutropenia, thrombocytopenia, and anemia were 21%, 19%, and 10%, respectively (Kantarjian et al., 2010). Cytophenias are associated with all BCR-ABL inhibitors (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010).

As with imatinib, potentially serious, nonhematologic side effects may occur and patients should be monitored. In a phase...
Identifying Side Effects of BCR-ABL Inhibitors

III study of previously treated patients, grade 3–4 fluid retention was reported in 4% of patients receiving dasatinib 100 mg daily, and grade 3–4 pleural effusion, fatigue, rash, and dyspnea were each reported in 2% in the patient group (Shah et al., 2010). Incidences of grade 3–4 fluid retention, pleural effusion, fatigue, and rash were 1% or lower in the phase III dasatinib front-line trial (Kantarjian et al., 2010). Any-grade pleural effusion was detected in 14% of patients treated with the 100 mg once daily dose versus 23% for those treated with 70 mg twice daily (Shah et al., 2010). In the dasatinib front-line trial, no grade 3–4 pleural effusion events were reported. Grade 1–2 pleural effusion was observed in 10% of patients, and manageable in all cases (Kantarjian et al., 2010). Patients receiving dasatinib therapy may develop fluid retention, manifesting as ascites, edema, and pleural and pericardial effusions. Grade 3–4 pleural effusion is more common in patients with advanced disease (Bristol-Myers Squibb, 2010).

Table 1. BCR-ABL Inhibitor Dose-Modification Guidelines for Management of Side Effects

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>IMATINIB</th>
<th>DASATINIB</th>
<th>NILOTINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Side Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML-AP, CML-BP, and Ph+ ALL</td>
<td>For an ANC &lt; 0.5 x 10⁹/L or platelets &lt; 10 x 10⁹/L:</td>
<td>For an ANC &lt; 0.5 x 10⁹/L or platelets &lt; 10 x 10⁹/L:</td>
<td>For ANC &lt; 1 x 10⁹/L or platelets &lt; 50 x 10⁹/L (CML-AP only):</td>
</tr>
<tr>
<td></td>
<td>• Check whether cytopenia is related to disease; if unrelated, reduce dose to 400 mg.</td>
<td>• Check whether cytopenia is related to disease; if unrelated, hold drug until ANC ≥ 1 x 10⁹/L and platelets ≥ 20 x 10⁹/L, then resume at starting dose.</td>
<td>• Hold drug until ANC &gt; 1 x 10⁹/L and platelets &gt; 50 x 10⁹/L, then resume drug at previous dose if recovery occurs in less than two weeks.</td>
</tr>
<tr>
<td></td>
<td>• If unresolved in two weeks, reduce to 300 mg.</td>
<td>• If cytopenia recurs, repeat first step and resume drug at 100 mg once daily (second episode) or 80 mg once daily (third episode).</td>
<td>• If low blood counts persist for more than two weeks, reduce dose to 400 mg once daily.</td>
</tr>
<tr>
<td></td>
<td>• If unresolved in four weeks, and is still unrelated to leukemia, hold drug until ANC ≥ 1 x 10⁹/L and platelets ≥ 20 x 10⁹/L, then resume at 300 mg.</td>
<td>• If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.</td>
<td></td>
</tr>
<tr>
<td>CML-CP</td>
<td>For an ANC &lt; 1 x 10⁹/L or platelets &lt; 50 x 10⁹/L:</td>
<td>For an ANC &lt; 0.5 x 10⁹/L or platelets &lt; 50 x 10⁹/L:</td>
<td>For an ANC &lt; 1 x 10⁹/L or platelets &lt; 50 x 10⁹/L:</td>
</tr>
<tr>
<td></td>
<td>• Hold drug until ANC ≥ 1.5 x 10⁹/L and platelets ≥ 75 x 10⁹/L, and then resume drug at previous dose.</td>
<td>• Hold drug until ANC ≥ 1 x 10⁹/L and platelets ≥ 50 x 10⁹/L, then resume drug at previous dose if recovery occurs in seven days or less.</td>
<td>• Hold drug until ANC &gt; 1 x 10⁹/L and platelets &gt; 50 x 10⁹/L, then resume drug at previous dose if recovery occurs in less than two weeks.</td>
</tr>
<tr>
<td></td>
<td>• If platelets &lt; 25 x 10⁹/L or ANC &lt; 0.5 x 10⁹/L recurs for more than seven days, repeat first step and resume drug at 80 mg once daily (second episode) or 50 mg once daily (third episode, first-line setting), or discontinue third episode, second-line setting.</td>
<td>• If platelets &lt; 25 x 10⁹/L or ANC &lt; 0.5 x 10⁹/L recurs for more than seven days, repeat first step and resume drug at 80 mg once daily (second episode) or 50 mg once daily (third episode).</td>
<td>• If low blood counts persist for more than two weeks, reduce dose to 400 mg once daily.</td>
</tr>
</tbody>
</table>

| **Nonhematologic Side Effects** | | | |
| Laboratory abnormalities | For bilirubin > 3 x ULN or liver transaminases > 5 x ULN: | – | For elevated bilirubin, liver transaminases, or serum lipase (grade 3 or higher): |
| | • Hold drug until bilirubin < 1.5 x ULN or liver transaminases > 2.5 x ULN, then continue at reduced dose. | – | • Hold drug and monitor serum levels, then resume at 400 mg once daily if event resolves to grade 1 or lower. |
| Nonspecific | If a severe event occurs, hold drug until resolved, then resume at dose appropriate to initial severity of event. | If a severe event occurs, hold drug until resolved or improved, then resume at dose appropriate to initial severity of event. | If a severe event or clinically significant event occurs, hold drug until resolved, then resume at 400 mg once daily; consider escalation to recommended starting dose if clinically appropriate. |
| QT prolongation | – | – | For a QTc > 480 ms: |
| | – | – | • Hold drug; correct serum potassium and magnesium if below normal limits; resume drug within two weeks at prior dose if QTcF returns to < 450 ms and < 20 ms of baseline. |
| | – | – | • If QTcF is 450–480 ms after two weeks, reduce dose to 400 mg once daily; discontinue if QTcF returns to > 480 ms. |
| | – | – | • Repeat ECG approximately seven days after any dose adjustment. |

ANC—absolute neutrophil count; AP—accelerated phase; BP—blast phase; CML—chronic myeloid leukemia; CP—chronic phase; ECG—electrocardiogram; ms—millisecond; Ph+ ALL—Philadelphia chromosome-positive acute lymphocytic leukemia; QTcF—Fridenrica-corrected QT interval; ULN—upper limit of normal.

Note: Based on information from Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010.
Hemorrhage is an additional side effect associated with dasatinib administration. Bleeding events predominantly occur (in more than 80% of cases) in the gastrointestinal tract. In all dasatinib clinical trials, severe gastrointestinal bleeding events, including fatalities, occurred in 4% of patients. Other severe bleeding events occurred in an additional 2% of patients (Bristol-Myers Squibb, 2010). Thrombocytopenia (p = 0.02) and advanced-phase CML (p = 0.03) are risk factors for bleeding events (Quintás-Cardama, Kantarjian, et al., 2009). The data suggest that patients with either or both of those risk factors should be monitored for bleeding complications. QT prolongation is rarely observed (QTcF greater than 500 ms, less than 1%) (Bristol-Myers Squibb, 2010).

Monitoring

As with imatinib, patients receiving dasatinib should be monitored vigilantly for signs or symptoms of emerging toxicities (Bristol-Myers Squibb, 2010; Galinsky & Buchanan, 2009; Novartis Pharmaceuticals, 2009, 2010). Of note, gastrointestinal tract and central nervous system bleeding may be associated with severe thrombocytopenia, and patients with a history of cardiac disease or hypertension are more likely to develop pleural effusion (Bristol-Myers Squibb, 2010; Quintás-Cardama et al., 2007). Patients should be counseled to promptly report symptoms of dyspnea or dry cough, and pleural effusion should be confirmed by chest radiograph.

Patient Counseling

Patients should be educated to report potential side effects, including fever, unusual bleeding or bruising, swelling, weight gain, increased shortness of breath, diarrhea, headache, nausea, vomiting, musculoskeletal pain, significant fatigue, or significant skin rash (Bristol-Myers Squibb, 2010). Patients also should report all other medications being taken, including over-the-counter supplements, as some medications may increase or decrease exposure to dasatinib. Similar to imatinib, dasatinib is metabolized primarily by hepatic CYP3A4 enzymes (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010). If a strong CYP3A4 inducer or inhibitor must be administered together with dasatinib, the dasatinib dose should be increased or decreased, respectively. Dose decreases to 20 mg daily are recommended for patients originally prescribed 100 mg daily, or to 40 mg daily for those originally prescribed 140 mg daily. Emerging toxicities should be monitored carefully and may necessitate pausing treatment with either dasatinib or the concomitant drug. Grapefruit juice also should be avoided (Bristol-Myers Squibb, 2010).

In addition to those drugs, caution also must be taken with antacids, histamine 2 blockers, and proton pump inhibitors (Bristol-Myers Squibb, 2010; NCCN, 2010). The solubility of dasatinib is pH dependent; therefore, concomitant administration of antacids and dasatinib must be avoided. If antacids must be taken, they should be administered two hours before or after dasatinib administration. Similarly, long-term suppression of gastric acid secretion by agents such as famotidine or omeprazole is likely to reduce dasatinib exposure. Therefore, antacids should be used in preference to histamine 2 blockers or proton pump inhibitors (Bristol-Myers Squibb, 2010; NCCN, 2010).

Management

Most side effects related to dasatinib may be managed through supportive measures and dose modification (Bristol-Myers Squibb, 2010). For hematologic side effects, growth factor support also may be indicated (NCCN, 2010; Quintás-Cardama, De Souza Santos, et al., 2009).

General fluid retention side effects may be managed using diuretics and supportive care (Bristol-Myers Squibb, 2010; NCCN, 2010). Patients exhibiting symptoms of pleural effusion should undergo a chest radiograph. Although most cases of pleural effusion may be managed with dose interruption (Bristol-Myers Squibb, 2010), diuretic agents and steroids also may be used, and severe cases may require thoracentesis and oxygen therapy (Bergeron et al., 2007; Bristol-Myers Squibb, 2010; NCCN, 2010; Quintás-Cardama et al., 2007; Rousselot et al., 2007).

Management steps for bleeding events include dose interruption and transfusion (Bristol-Myers Squibb, 2010; Quintás-Cardama, Kantarjian, et al., 2009). Skin rash may be specifically managed with topical or systemic steroids (NCCN, 2010). In case of nausea, the medication should be taken with a meal and a large glass of water (NCCN, 2010). Supportive care is recommended in the case of diarrhea (NCCN, 2010).

Dasatinib should be administered with caution to any patient at risk for cardiac issues (specifically prolongation of the QT interval). Hypokalemia and hypomagnesemia must be corrected before administration (Bristol-Myers Squibb, 2010). Healthcare practitioners should be aware that dasatinib tablets contain lactose and, therefore, are not recommended in patients with hereditary galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption.

Nilotinib

Safety Profile

Nilotinib is approved for front-line treatment in patients with CML-CP at a dosage of 300 mg twice daily and at a dosage of 400 mg twice daily for patients with CML-CP or -AP intolerant of or resistant to prior therapy, including imatinib (Novartis Pharmaceuticals, 2010). Management of side effects is generally through dose adjustment and supportive measures (NCCN, 2010; Novartis Pharmaceuticals, 2010).

Nonhematologic cross-intolerance with imatinib (defined as the recurrence of a grade 3–4 side effect during nilotinib treatment that led to the discontinuation of imatinib) is minimal; however, 55% of patients with hematologic intolerance to imatinib experienced the same persistent grade 2 events, or grade 3–4 events to nilotinib (Cortes et al., 2011).

In the phase II study that led to the approval of nilotinib in previously treated patients, the most frequent side effects were, as for other BCR-ABL inhibitors, hematologic. After a minimum of 19 months of follow-up, grade 3–4 neutropenia, thrombocytopenia, and anemia were observed in 31%, 51%, and 10% of patients,

Women of childbearing potential receiving dasatinib should avoid pregnancy (Bristol-Myers Squibb, 2010). Men receiving dasatinib, or their partners, are recommended to use contraception to prevent pregnancy.
Table 2. Monitoring Recommendations for Treatment With BCR-ABL Inhibitors

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>IMATINIB</th>
<th>DASATINIB</th>
<th>NILOTINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding-related events</td>
<td>Use with caution in patients taking anticoagulants or medications that inhibit platelet function, such as warfarin, because plasma levels may be affected by drug.</td>
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<td>Use with caution in patients taking anticoagulants or medications that inhibit platelet function, such as warfarin, because plasma levels may be affected by drug.</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>CBCs weekly for month 1, every two weeks for month 2, then periodically as indicated</td>
<td>CBCs weekly for months 1 and 2, then monthly or periodically as indicated</td>
<td>CBCs every two weeks for months 1 and 2, then monthly or periodically as indicated</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>–</td>
<td>–</td>
<td>Periodic serum potassium, magnesium, phosphorus, and calcium level checks</td>
</tr>
<tr>
<td>Elevated serum lipase level</td>
<td>–</td>
<td>–</td>
<td>Use carefully in case of history of pancreatitis; monthly serum lipase level checks, or as indicated.</td>
</tr>
<tr>
<td>Fluid retention and edema</td>
<td>Regularly weigh and monitor for signs and symptoms; carefully investigate rapid weight gain.</td>
<td>Chest radiographs in case of pleural effusion symptoms (e.g., dyspnea, dry cough)</td>
<td>–</td>
</tr>
<tr>
<td>Hepatotoxicity and impairment</td>
<td>Liver function checks before treatment start, monthly, and as indicated</td>
<td>–</td>
<td>Monthly hepatic function checks, or as clinically indicated</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Carefully monitor patients’ TSH levels after thyroidectomy and with levothyroxine replacement.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>–</td>
<td>Administer with care to patients at risk, such as those with hypokalemia, hypomagnesemia, or congenital long QT syndrome; or those taking drugs that cause QT prolongation, including antiarrhythmic medication or cumulative anthracycline therapy.</td>
<td>Periodic serum potassium and magnesium level checks; ECGs at baseline, after seven days of treatment, and periodically thereafter or after dose adjustments. Closely monitor patients with hepatic impairment.</td>
</tr>
<tr>
<td>Severe CHF and left ventricular dysfunction</td>
<td>Carefully monitor patients with cardiovascular disease or at risk for cardiac failure.</td>
<td>Monitor patients for signs or symptoms.</td>
<td>Carefully monitor patients with cardiovascular disease or at risk for cardiac failure.</td>
</tr>
</tbody>
</table>

CBCs—complete blood counts; CHF—congestive heart failure; ECGs—electrocardiograms; TSH—thyroid-stimulating hormone

Note. Based on information from Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010.

respectively (Kantarjian et al., 2009). Grade 3–4 nonhematologic side effects were less frequent. The most common side effects in the phase II study were rash (2%), headache (2%), and diarrhea (2%) (Kantarjian et al., 2009). In the phase III front-line trial of nilotinib, grade 3–4 neutropenia and thrombocytopenia were reported in 12% and 10% of patients, respectively, at the lower dosage of 300 mg twice daily (Saglio et al., 2010). A risk also exists for less common but potentially serious side effects, the most serious of which is QT prolongation and sudden death (0.6% of patients in an ongoing study), which is indicated by a black box warning in the nilotinib prescribing information (Novartis Pharmaceuticals, 2010). A fasting requirement is necessary for nilotinib administration to mitigate those risks. Nilotinib use also may result in serum lipase elevation, liver function abnormality, hepatic impairment, and electrolyte abnormalities (Novartis Pharmaceuticals, 2010).

Monitoring

As with other BCR-ABL inhibitors, patients receiving nilotinib must be vigilantly monitored for a number of adverse events (Bristol-Myers Squibb, 2010; Galinsky & Buchanan, 2009; Novartis Pharmaceuticals, 2009, 2010). Oncology nurses should be aware of the potential for cardiac abnormalities, and particular vigilance is required for monitoring QT prolongation.

An electrocardiogram should be performed at baseline, after seven days of treatment, and periodically throughout therapy. Of note, nilotinib is contraindicated (the only BCR-ABL inhibitor to be so) in patients with long QT syndrome, hypokalemia, or hypomagnesemia. Electrolyte levels should be evaluated at the start of nilotinib therapy and reassessed periodically (Novartis Pharmaceuticals, 2010).

Patient Counseling

Patients should be educated to report potential major side effects, including an irregular heartbeat, feeling faint or light headed, unexplained bleeding or bruising, blood in urine or stool, unexplained weakness, yellow skin and eyes, sudden headache, changes in vision, confusion, unconsciousness, and sudden stomach area pain with nausea and vomiting (Novartis...
Pharmaceuticals, 2010). Before starting nilotinib, a medical history and examination should determine the presence of heart problems, an irregular heartbeat, QT prolongation (or family history), liver problems, pancreatitis, low serum potassium or magnesium levels, or severe problems with lactose or other sugars (Novartis Pharmaceuticals, 2010).

The patient should report all other medications being taken, including over-the-counter supplements. As with imatinib and dasatinib, nilotinib is metabolized primarily by hepatic CYP3A4 enzymes (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010). If a strong CYP3A4 inhibitor must be coprescribed with nilotinib, the dose should be reduced to 300 mg once daily, and a washout period for the CYP3A4 inhibitor must be allowed following its discontinuation before the original dose of nilotinib is resumed. Grapefruit products also should be avoided (Novartis Pharmaceuticals, 2010).

Caution is warranted in the concomitant administration of nilotinib and warfarin. Warfarin is a sensitive substrate for hepatic CYP2C9, which nilotinib has been shown to inhibit in a competitive manner (Kaminsky & Zhang, 1997; Novartis Pharmaceuticals, 2010). Although initial data from a study indicate that nilotinib has no effects on the pharmacokinetics or pharmacodynamics of warfarin (Yin et al., 2009), monitoring still is advisable. Women of childbearing potential receiving nilotinib should avoid pregnancy (Novartis Pharmaceuticals, 2010). Men receiving dasatinib, and their partners, are recommended to use contraception to prevent pregnancy.

Management

Most side effects can be managed through dose modification (Bristol-Myers Squibb, 2010; Novartis Pharmaceuticals, 2009, 2010) and supportive measures (Novartis Pharmaceuticals, 2010; NCCN, 2010). In the case of hematologic side effects, growth factor support also may be indicated (NCCN, 2010). In general, grade 3 nonhematologic side effects are treated by using specific interventions. Management steps for rash include use of topical or systemic steroids (NCCN, 2010). To avoid QT interval prolongation, hypokalemia and hypomagnesemia should be corrected before administration, and drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided (Novartis Pharmaceuticals, 2010). In addition, a strict fasting requirement must be observed to avoid rises in nilotinib bioavailability (Novartis Pharmacuetical, 2010; NCCN, 2010).

Because the capsules contain lactose, nilotinib is not recommended in patients with hereditary galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption (Novartis Pharmaceuticals, 2010).

Conclusion

BCR-ABL inhibitors are subject to a number of potentially serious side effects. Clinical intolerance to a BCR-ABL inhibitor occurs when the toxicity of the compound outweighs the clinical benefit provided by that compound at the current dose. Intolerance to BCR-ABL inhibitors may lead to dose adjustment or decreased adherence. In an effort to avoid such intolerance, patients should be thoroughly screened for the presence of risk factors for adverse events, including a review of all medications. If a strong CYP3A4 inducer or inhibitor must be administered together with a BCR-ABL inhibitor, the BCR-ABL inhibitor dose should be increased or decreased, respectively. Patients should be counseled to report key toxicities to their nurse or physician.

Patients also should be vigilantly monitored during treatment for signs or symptoms of emerging toxicities. Patients at risk of serious side effects should be monitored particularly closely. Early intervention may reduce the need for dose adjustment or interruption and ensure adherence at the prescribed dose. Effective management of toxicities also can reduce the risk of switching to other treatment.

Most side effects associated with BCR-ABL inhibitor treatment of patients with CML are noneverse, manageable, and reversible—managed through dose modification and supportive measures. However, serious side effects may require an interruption or cessation of treatment. Discontinuation of imatinib, as with other BCR-ABL inhibitors, is recommended in the event of an unresponsive grade 3 or any grade 4 nonhematologic side effect. Patients who discontinue imatinib therapy may be switched to dasatinib or nilotinib therapy.

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