Dasatinib, an oral inhibitor of multiple tyrosine kinases, including BCR-ABL, Src, and platelet-derived growth factor receptor, was approved for patients with imatinib-resistant or -intolerant chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL). Dasatinib demonstrated efficacy with a well-tolerated safety profile in all phases of CML and Ph+ ALL, which led to its 2006 approval by the U.S. Food and Drug Administration for clinical use. However, although most adverse events are grade 1 or 2, a number of adverse events require management and monitoring to ensure that patients can continue receiving the treatment. This review discusses the appropriate nursing management of key adverse events (cytopenias, fluid retention, bleeding, gastrointestinal toxicity, and cardiotoxicity) to ensure that patients gain maximum benefit from this multitargeted agent.

**At a Glance**

- Adverse events related to dasatinib therapy require management and monitoring to maximize patient benefit.
- Cytopenias, fluid retention, bleeding, gastrointestinal toxicity, and cardiotoxicity require the most vigilance and potential intervention.
- Nurses should be aware of potential drug-drug interactions with dasatinib.
imatinib and/or interferon alpha and may have had low-normal or lower-than-normal blood counts when starting therapy. Other grade 3 or 4 adverse events included pleural effusion in 6% (see Table 1) (Gambacorti et al., 2007; Guilhot et al., 2007; Ottmann et al., 2007; Stone et al.).

The dasatinib dose of 70 mg twice daily was chosen because of the sustained inhibition of BCR-ABL. In a large, randomized, multi-center, phase III study, patients with imatinib-resistant or -intolerant CP CML were treated with four dasatinib doses to determine the optimal dasatinib dose: the “standard” approved dose of 70 mg twice daily, 140 mg once daily, 50 mg twice daily, and 100 mg once daily (Hochhaus et al., 2007). Of particular interest were the data from the 100 mg once-daily arm. Although efficacy was similar across all four doses, 100 mg once daily was associated with statistically significant reductions in thrombocytopenia and pleural effusions, compared with all other doses evaluated. Significantly fewer patients treated with 100 mg once daily experienced grade 3 or 4 adverse events than patients receiving the 70 mg twice-daily dose (30% versus 48%; p < 0.001). Grade 3 or 4 thrombocytopenia with 100 mg once daily was 22% relative to 37% for the 70 mg twice daily arm (p < 0.004). Significantly fewer patients experienced pleural effusions (of any grade) with dasatinib 100 mg once daily than with 70 mg twice daily (7% versus 16%; p < 0.024). Although the follow-up in the trial was short (11.5 months), 100 mg once-daily dasatinib was approved in 2007 for use in patients with CP CML based on the data.

In a trial comparing dasatinib and high-dose imatinib (800 mg per day) in patients with resistance to imatinib at a dose of 400 mg per day, dasatinib showed improved complete cytogenetic response rates (40% and 16%, respectively; p = 0.004) and increased progression-free survival (hazard ratio = 0.14; p < 0.0001) relative to high-dose imatinib (Kantarjian, Pasquini, et al., 2007; Kantarjian, Rousselot, et al., 2007). (Complete cytogenetic response is defined as zero Ph+ bone-marrow cells when at least 20 are analyzed.) Clear differences existed in the tolerability profile of the two agents, with patients receiving imatinib experiencing increased superficial edema (45% versus 15% with dasatinib) and fluid retention (45% versus 30% with dasatinib) and patients receiving dasatinib experiencing more pleural effusions (17% versus 0% with imatinib) and cytopenias. Cytopenias in the dasatinib treatment group relative to high-dose imatinib were as follows: grade 3 or 4 neutropenia: 61% versus 39%; grade 3 or 4 thrombocytopenia: 56% versus 14%. These were reversible and manageable with dose adjustments.

In START-A, which evaluated 174 patients with AP CML, the most common grade 3 and 4 adverse events were neutropenia and thrombocytopenia, occurring in 76% and 82% of patients, respectively (Guilhot et al., 2007). Similar data with imatinib suggest that patients in later phases of disease experience an increased incidence of adverse events, given the likelihood of extensive prior therapy (Gambacorti et al., 2007; Stone et al.).

Additional data on dasatinib adverse events, provided in the dasatinib prescribing information, were collated from 911 patients in dasatinib clinical trials and included the following serious adverse events: pyrexia (9%), pleural effusion (8%), febrile neutropenia (7%), gastrointestinal bleeding (6%), pneumonia (6%), anemia (3%), cardiac failure (3%), and diarrhea (2%) (Bristol-Myers Squibb, 2006).
The efficacy data, combined with low toxicity, demonstrate that dasatinib has a favorable risk-benefit profile for patients who are imatinib-resistant or -intolerant. Although most adverse events are grade 1 or 2 (Gambacorti et al., 2007; Guilhot et al., 2007; Ottmann et al., 2007; Stone et al.), most likely because of a high incidence of pancytopenia prior to therapy. However, an exception applies to patients with AP or BC CML or Ph+ ALL, compared with patients with CP CML (Guilhot et al.; Ottmann et al.; Stone et al.), most likely because of a high incidence of pancytopenia prior to therapy.

The first step for managing cytopenias for patients with CP CML is temporary interruption of dasatinib and careful monitoring until resolution of the specific cytopenia. Resolution is described as an absolute neutrophil count (ANC) of higher than 1,000/mm³ and platelets higher than 50,000/mm³ in patients with CP CML, and higher than 20,000/mm³ in patients with AP CML or Ph+ ALL (Bristol-Myers Squibb, 2006) (see Table 2). Following resolution of blood counts, treatment with dasatinib can be continued at the original 100 mg once-daily starting dose for patients with CP CML. If another reduction in platelets occurs less than 25,000/mm³ or a recurrence of ANC less than 500/mm³ for more than seven days, patients should have treatment interrupted as described previously, and resumption of dasatinib therapy should be at the reduced dose of 80 mg once daily after a second episode, or stopped altogether after a third episode. However, an exception applies to patients with AP or BC CML or Ph+ ALL. Many such patients can have cytopenias that occur during the first month of therapy, most likely sequelae from their disease that may present even before therapy, rather than treatment-related events (Sawyers, 1999). Nurses should make this distinction whenever possible to avoid delaying treatment. In specific cases of continuing dasatinib treatment despite

### Management of Specific Adverse Events

#### Cytopenias

The incidence of neutropenia and thrombocytopenia was 49% and 48% for patients with CP CML, 76% and 82% for patients with AP CML, and 78% and 78% for patients with Ph+ ALL. The relatively high incidence of dasatinib-associated cytopenias has no single cause (Guilhot et al., 2007; Ottmann et al., 2007; Stone et al., 2007), but they are most likely caused by a number of factors, including the suppressive effect of dasatinib on hematopoietic stem cell proliferation, the disease state, and prior therapies received by patients. Cytopenias usually occur within the first one or two months of dasatinib treatment. Cytopenias occur more commonly in patients with AP or BC CML or Ph+ ALL, compared with patients with CP CML (Guilhot et al.; Ottmann et al.; Stone et al.), most likely because of a high incidence of pancytopenia prior to therapy.

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>CHRONIC PHASE CML</th>
<th>ACCELERATED PHASE CML</th>
<th>MYELOID BLAST CRISIS OR LYMPHOID BLAST CRISIS CML</th>
<th>PH+ ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (grade 3: absolute neutrophil count higher than 500 mm³ but less than 1,000/mm³; grade 4: ANC less than 500/mm³)</td>
<td>49</td>
<td>76</td>
<td>Not applicable</td>
<td>78</td>
</tr>
<tr>
<td>Thrombocytopenia (grade 3: platelets 25,000–50,000/mm³; grade 4: platelets less than 25,000/mm³)</td>
<td>48</td>
<td>82</td>
<td>Not applicable</td>
<td>78</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any grade</td>
<td>27</td>
<td>27</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>• Grade 3 or 4 (grade 3: symptomatic, requiring supplemental oxygen, more than two therapeutic thoracenteses, tube drainage, or pleurodesis indicated; grade 4: life threatening)</td>
<td>6</td>
<td>5</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any grade</td>
<td>37</td>
<td>52</td>
<td>Not applicable</td>
<td>33</td>
</tr>
<tr>
<td>• Grade 3 or 4 (grade 3: increase of seven or more stools per day over baseline, incontinence, IV fluids for 24 hours or more, hospitalization, severe increase in ostomy output compared to baseline, interfering with activities of daily living; grade 4: life threatening)</td>
<td>Not applicable</td>
<td>8</td>
<td>Not applicable</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any grade</td>
<td>Not applicable</td>
<td>28</td>
<td>Not applicable</td>
<td>22</td>
</tr>
<tr>
<td>• Grade 3 or 4 (grade 3: inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated for 24 hours or more; grade 4: life threatening)</td>
<td>Not applicable</td>
<td>Less than 1</td>
<td>Not applicable</td>
<td>–</td>
</tr>
</tbody>
</table>

*Note. Based on information from Gambacorti et al., 2007; Guilhot et al., 2007; Ottmann et al., 2007; Stone et al., 2007.*
cytopenia, the authors recommend close monitoring and more frequent complete blood count assessments (e.g., weekly until blood counts stabilize).

Data also have shown the potential of growth-factor support in patients experiencing cytopenias (Quintas-Cardama, Kantarjian, Nicaise, et al., 2006). Although it was evaluated in a single-center study, seven of seven patients experienced improved ANC of higher than 2 x 10^9/L (2,000/mm^3) when treated with granulocyte-colony stimulating factor (G-CSF) 300 mcg daily for two to seven days each week. The median time to G-CSF response was 10 days; importantly, the patients experienced less time off dasatinib treatment after they began receiving G-CSF compared with before G-CSF initiation. In addition, 9 of 15 patients receiving erythropoietin achieved hemoglobin increase of at least 2 g/dl.

The authors have treated patients who required a dose reduction because of grade 3 or 4 cytopenias, and those patients have subsequently shown early signs of disease progression. In such instances, returning to the original dose of dasatinib did not lead to a recurrence of cytopenias. This has been variable, but in those circumstances when the cytopenias did return, after resolution and a dose reduction, the events were corrected.

### Nonhematologic Adverse Events

Management of nonhematologic adverse events usually is determined on a case-by-case basis, although general dose modification principles apply. If a severe, grade 3 (National Cancer Institute, 2008) nonhematologic adverse reaction develops with dasatinib use, treatment must be withheld until the event has resolved or improved to less than grade 1. Thereafter, treatment can be resumed as appropriate at a reduced dose, depending on the initial severity of the event. The dose of dasatinib can be increased or reduced in 20 mg increments, based on individual safety and tolerability.

### Fluid Retention

Fluid retention events, including pleural effusion, are some of the most frequently occurring nonhematologic toxicities observed with dasatinib (Gambacorti et al., 2007; Guilhot et al., 2007; Ottmann et al., 2007; Stone et al., 2007). The underlying cause of the adverse events is yet to be identified; however, data from some reports suggest that the potent inhibition of PDGFR by dasatinib may play a role (Chen, Lee, Bhalla, & Wu, 2006; Jayson et al., 2005).

Among the 911 patients included in the data in the dasatinib prescribing information (patient population combined from five phase II trials and one phase I study), most superficial and pleural effusions were grade 1 or 2. Severe fluid retention (grade 3 or 4, including pleural and pericardial effusion) was reported in 5% and 1% of patients, respectively (Bristol-Myers Squibb, 2006).

Symptoms suggestive of pleural effusion, such as dyspnea, dry cough, or abnormal oxygen levels in the blood, should result in a chest x-ray to confirm diagnosis. The evaluation not only allows for an accurate assessment of fluid retention but also serves as a baseline for subsequent assessments to evaluate management. If pleural effusion is identified, the standard management approach is to hold dasatinib until resolution. In cases where an adverse event does not resolve within seven days, the authors' institution has used diuretic treatment with success. In patients presenting with severe fluid retention, the institution has used diuretics before waiting the suggested seven days. Oxygen requirement was not common. The need for therapeutic thoracentesis was seen and controlled the event.

Based on anecdotal experience, some centers advocate the use of steroidal therapy for patients with pleural effusions. Although the approach is not standard, Quintas-Cardama, Kantarjian, Munden, et al. (2006) showed that prednisone was an effective treatment in patients with pleural effusion. If steroids

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**Table 2. Dose Modification Guidelines for Patients With Chronic Myeloid Leukemia (CML) or Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Who Experience Neutropenia or Thrombocytopenia With Dasatinib**

<table>
<thead>
<tr>
<th>DISEASE PHASE</th>
<th>STARTING DOSE OF DASATINIB</th>
<th>ABSOLUTE NEUTROPHIL COUNT (ANC) AND PLATELET COUNT</th>
<th>DOSE ADJUSTMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic phase CML</td>
<td>70 mg twice daily</td>
<td>ANC less than 500/mm^3 and/or platelets less than 50,000/mm^3</td>
<td>Stop dasatinib until ANC is 1 x 10^9/L (1,000/mm^3) or higher and platelets are 50 x 10^9/L (50,000/mm^3) or higher. Resume treatment with dasatinib at the original starting dose. If platelets are less than 25 x 10^9/L (25,000/mm^3) and/or recurrence of ANC less than 0.5 x 10^9/L (500/mm^3) for more than seven days, repeat step one and resume dasatinib at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode).</td>
</tr>
<tr>
<td>Accelerated phase CML, blast phase CML, and Ph+ ALL</td>
<td>70 mg twice daily</td>
<td>ANC less than 500/mm^3 and/or platelets less than 10,000/mm^3</td>
<td>Check if cytopenia is related to leukemia (marrow aspirate or biopsy). If cytopenia is unrelated to leukemia, stop dasatinib until ANC is 1 x 10^9/L (1,000/mm^3) or higher and platelets are 20 x 10^9/L (20,000/mm^3) or higher, then resume at the original starting dose. If recurrence of cytopenia, repeat step one and resume dasatinib at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). If cytopenia is related to leukemia, consider dose escalation to 100 mg twice daily.</td>
</tr>
</tbody>
</table>

*Note. Based on information from Bristol-Myers Squibb, 2006.*
are used, the current authors recommend a short course of pulse dose steroids and tapering. Choosing between interrupting therapy and administering diuretics or steroids should be based on the general health and clinical situation of each individual patient.

**Bleeding-Related Events**

A low incidence of bleeding-related events (10%) has been reported with dasatinib, and they are usually associated with development of thrombocytopenia. Despite the low frequency of severe bleeding, the known complication of gastrointestinal (GI) and central nervous system (CNS) bleeds in patients with leukemia means that ongoing standard monitoring for such events is required. Weekly complete blood counts until blood counts normalize is prudent practice. Severe CNS hemorrhages, including fatalities, and severe GI hemorrhages occurred in 1% and 7% of patients receiving dasatinib, respectively (Bristol-Myers Squibb, 2006).

The risk of bleeding is elevated in patients requiring treatment with anticoagulants, and the authors recommend the current standard of care, warfarin (Coumadin®, Bristol-Myers Squibb), rather than low-molecular-weight heparin or similar treatments that profoundly inhibit platelet function and are difficult to monitor. Such patients should be monitored frequently for any symptoms of GI or CNS hemorrhage.

Management of bleeding in patients receiving dasatinib should include regular blood count testing (weekly for the first two months of treatment), and patients should be informed of the importance of notifying their healthcare providers of any form of bleeding or bruising. Dasatinib dose modifications also may be performed when patients experience thrombocytopenia (described previously). In the case of severe GI hemorrhages, treatment must be interrupted, and red blood cell transfusion may be appropriate.

**Gastrointestinal Adverse Events**

Grade 1 and 2 GI disorders, including diarrhea, nausea, and vomiting, were observed frequently with dasatinib (Guilhot et al., 2007; Ottmann et al., 2007; Stone et al., 2007). The incidence of any grade diarrhea was 31%, nausea 22%, and vomiting 13% when collated among all clinical studies (Bristol-Myers Squibb, 2006). In the authors’ practice, management of these mild to moderate adverse events involves anti diarrheal and antiemetic medications. However, based on early-phase observations when patient fasting resulted in increased nausea, the authors found that cases would resolve when patients were allowed to eat after initial fasting periods. Therefore, they recommend administering dasatinib after food and a glass of water. In the case of more severe GI adverse events (grade 3 or higher) that are not responsive to therapy, the dose should be withheld. Following resolution of the event, dose reduction should be considered.

**Cardiotoxicity and QTc Prolongation**

Dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval) according to in vitro data (Bristol-Myers Squibb, 2006). Among patients with CML treated with dasatinib in single-arm clinical studies, the mean QTc interval changes, calculated with Fridericia’s method (QTcF), were 3–6 msec (normal is 420 msec). Overall, nine patients experienced QTc prolongation, with three patients (less than 1%) experiencing a QTcF higher than 500 msec, the most clinically relevant measurement of cardiac toxicity (Bristol-Myers Squibb).

According to Bristol-Myers Squibb (2006), the incidence of severe cardiac failure in 911 patients from phase I and II studies is 3%, which is consistent with that observed with imatinib. Dasatinib should be administered with caution to patients who have or may develop QTc prolongation, including patients with hypokalemia or hypomagnesemia (congenital long QT syndrome), patients taking antiarrhythmic medication or other therapies that potentially prolong the QT interval, and patients who may have received cumulative high-dose anthracycline therapy. However, electrocardiogram (EKG) is not required with all patients prior to therapy, although a baseline EKG may be warranted based on anecdotal observations. The authors suggest that all patients have a baseline EKG prior to starting this medication. EKG and multigated acquisition scans are not standard prior to initiation of dasatinib but may be considered if medically indicated. In patients who develop QTc prolongation, treatment should be withheld until the event has resolved. Dasatinib treatment may be resumed at a reduced dose, but regular monitoring is recommended.

**Skin Rash**

Rash and other skin toxicities have been associated with tyrosine kinase inhibitors (Esper, Gale, & Muchibauer, 2007). The following toxicities have been grouped under rash: erythema, exfoliative rash, generalized erythema, miliaria, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, systemic lupus erythematosus rash, urticaria vesiculosa, drug eruption, and rash vesicular. In a large randomized trial of treatment-naive patients with CP CML who received imatinib, 34% experienced these adverse events (O’Brien et al., 2005). Pooled data from 911 patients who received dasatinib showed that 35% of patients had all-grade toxicity and 1% experienced grade 3 or 4 (Bristol-Myers Squibb, 2006). Rash generally can be managed with emollients to minimize symptoms and alleviate discomfort. The authors do not recommend prophylactic administration of dermatologic therapies. They recommend monitoring and treating on a case-by-case basis.

**Drug-Drug Interactions**

As an inhibitor of CYP3A4, dasatinib may decrease the metabolic clearance of drugs that are metabolized primarily by CYP3A4 (Bristol-Myers Squibb, 2006). Therefore, CYP3A4 substrates should be administered with caution in patients receiving dasatinib (see Figure 1). The appropriate course of action for patients requiring concomitant use of drugs that inhibit CYP3A4 is to monitor patients closely for symptoms of toxicity, such as neutropenia and thrombocytopenia.

Conversely, drugs that induce CYP3A4 activity may decrease plasma concentrations of dasatinib, and alternative agents with less enzyme induction potential should be used. A five-fold decrease in the plasma concentration of dasatinib has been
observed with concomitant administration of rifampicin (Bristol-Myers Squibb, 2006). Therefore, if dasatinib is administered with a CYP3A4 inducer, increasing the dose of dasatinib should be considered, and patients should be carefully monitored for toxicity. Another alternative would be to substitute the CYP3A4 inducer with a concurrent drug with less enzyme-inducing potential.

Other substances that may decrease dasatinib plasma concentrations include St. John’s wort, antacids, and long-term gastric acid suppressors such as H2 blockers and proton-pump inhibitors. In the case of proton-pump inhibitors, such agents should be administered when no alternative therapy is possible and 12 hours prior to or after dasatinib. In all other cases, the authors recommend switching to alternative antacid therapies if H2 blockers and proton-pump inhibitors are not strictly required; administration of these should occur 12 hours prior to or after dasatinib as well.

**Patient Information**

Prior to commencing therapy with dasatinib, patients should provide a detailed list of all concurrent medications they are taking, including prescriptions, over-the-counter medicines, vitamins, antacids, and herbal supplements to avoid drug-drug interactions.

Patients also should be educated to identify and report symptoms of adverse events so they can be addressed promptly. Although the protocol at each center may differ, patients should notify their healthcare providers immediately if they develop a fever, swelling, weight gain, increasing shortness of breath, or bleeding or easy bruising while taking dasatinib.

**Conclusion**

Overcoming resistance and intolerance to imatinib mesylate in patients with CML is a key clinical challenge. The hematologic and cytogenetic responses achieved in imatinib-resistant and -intolerant CML and Ph+ ALL demonstrate that dasatinib has the potential to overcome such issues.

Data from multicenter, international clinical trials show that dasatinib has a manageable and reversible safety profile. Key toxicities to be aware of when using dasatinib in the treatment of CML or Ph+ ALL are cytopenias, fluid retention including pleural effusions, bleeding, GI toxicities, and QTc prolongation. To identify these adverse events, monitor laboratory parameters, conduct physical assessments, and educate patients to minimize potential side effects and maximize patient benefit. For patients unable to tolerate dasatinib, nilotinib is another tyrosine kinase inhibitor therapy available for the treatment of CML.

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**References**


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