Lenalidomide is an immunomodulatory drug that has shown preliminary activity in the treatment of chronic lymphocytic leukemia (CLL). Much is known about the safety profile of lenalidomide from experience in other hematologic malignancies, such as myelodysplastic syndromes and multiple myeloma. In addition to the known adverse effects associated with lenalidomide (e.g., myelosuppression, rash, fatigue), some unique effects (e.g., tumor flare reactions, tumor lysis syndrome) have arisen during clinical studies of CLL. Typical signs of tumor flare reactions include early onset of painful enlargement of the lymph nodes or spleen, with or without low-grade fever, rash, and bone pain. Management may require nonsteroidal anti-inflammatory drugs or a short course of corticosteroids. Dose delays or reductions usually are not required for tumor flare reactions. Signs of tumor lysis syndrome may include shortness of breath, peripheral edema, generalized weakness, sweating, fever, and tachycardia. Untreated tumor lysis syndrome can result in renal impairment and congestive heart failure. Careful monitoring and appropriate management of treatment-related side effects can help ensure that patients with CLL achieve maximum therapeutic benefit from lenalidomide therapy.

**At a Glance**

- Ongoing clinical trials continue to investigate the efficacy and disease-specific side effects of lenalidomide.
- The use of lenalidomide in chronic lymphocytic leukemia (CLL) may result in tumor flare reaction and tumor lysis syndrome, which can be managed with appropriate prophylaxis, monitoring, and treatment.
- With proper monitoring, particularly in the first cycles of therapy, lenalidomide can be administered safely in CLL, resulting in minimal dose interruption or reductions.

**Kena C. Miller, RN, MSN, FNP, Laurie Musial, RN, BSN, CCRP, Amy Whitworth, RN, BSN, and Asher Chanan-Khan, MD**

Chronic lymphocytic leukemia (CLL), a malignant disorder of the lymphocytes, is one of the most common forms of leukemia in the United States. An estimated 15,490 new cases of CLL were diagnosed in the United States in 2009, and about 4,390 people died from CLL (Jemal et al., 2009). The incidence of CLL increases with age, and men are more likely to develop the disorder. The disease also is slightly more prevalent in Caucasians than in African Americans (Redaelli, Laskin, Stephens, Botteman, & Pashos, 2004).

Diagnosis of CLL is based on clinical examination and specific tests on the peripheral blood and bone marrow. Flow cytometry is helpful in diagnosing CLL and ruling out other lymphoproliferative disorders. Signs and symptoms of CLL usually develop slowly, with many patients being asymptomatic during the early stages of the disease. Common symptoms include fatigue, shortness of breath, swollen lymph nodes, repeated infections, and unintended weight loss.

In general, patients with CLL do not require treatment until they develop symptoms or experience disease progression (Hallek et al., 2008). Approved treatments include purine analogs (such as fludarabine), bendamustine, alkylating agents (such as chlorambucil or cyclophosphamide), or various combinations (Catovsky et al., 2007; Eichhorst et al., 2006; Flinn et al., 2007; Rai et al., 2000). The anti-CD20 monoclonal antibody rituximab appears to improve outcomes when added to fludarabine-based chemotherapy.
in the first-line setting (Byrd et al., 2003; Keating et al., 2005; Tam et al., 2008), and in patients with relapsed or refractory disease (Robak et al., 2008; Wierda et al., 2005). Alemtuzumab, a monoclonal antibody that targets CD52 on the surface of mature lymphocytes, also has been approved by the U.S. Food and Drug Administration (FDA) for use as first-line monotherapy in patients with CLL with a deletion 17p cytogenetic abnormality (del(17p)). Alemtuzumab also has FDA approval as first-line monotherapy in patients with CLL aged 70 years or older without del(17p) and as second-line therapy in patients with CLL younger than 70 without del(17p) (National Comprehensive Cancer Network [NCCN], 2008). An anti-CD20 monoclonal antibody, ofatumumab, was approved in 2009 for treatment of patients with CLL refractory to fludarabine or alemtuzumab (FDA, 2009).

Lenalidomide (Revlimid®, Celgene Corporation) is an immunomodulatory agent with anticancer properties (Corral et al., 1996). Lenalidomide was approved by the FDA (2005, 2006) for treating patients with myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality and in combination with dexamethasone in patients with previously treated multiple myeloma. Because of its activity in multiple myeloma, lenalidomide also has been investigated in other B-cell malignancies, including CLL. Lenalidomide is noted to have antileukemic effects in patients with CLL; studies evaluating lenalidomide have reported overall response rates ranging from 30%–50% in patients with relapsed or refractory CLL (Chanan-Khan et al., 2006; Ferrajoli et al., 2008) and 65% in patients with previously untreated, symptomatic CLL (Chen et al., 2008).

Lenalidomide offers more potent immunomodulatory effects when compared with thalidomide (Muller et al., 1999). However, lenalidomide is associated with some events that require close monitoring and, in some cases, intervention (see Tables 1 and 2). In clinical trials, the use of lenalidomide in patients with CLL has revealed some safety considerations that may be specific to CLL, such as tumor flare reaction and tumor lysis syndrome. With appropriate prophylaxis, monitoring, and management, the events can be managed safely without discontinuation of lenalidomide therapy. The aims of this review are (a) to describe the adverse events nurses are likely to encounter in patients with CLL who are receiving lenalidomide and (b) to provide recommendations and guidance on how to monitor and optimally manage patients so that lenalidomide therapy can continue safely to achieve maximum therapeutic outcomes.

**Lenalidomide in Relapsed or Refractory Chronic Lymphocytic Leukemia**

**Roswell Park Cancer Institute Study**

A phase II study of lenalidomide (Chanan-Khan et al., 2006) conducted at Roswell Park Cancer Institute (RPCI), the authors’ institution, enrolled 45 patients with relapsed or refractory CLL. Median age was 64 years (range 42–75 years), and 29 patients (64%) had advanced-stage disease (Rai stage III or IV). The median number of prior therapies was 3 (range 1–10), and 23 patients (51%) were refractory to fludarabine. Most patients (n = 38, 84%) also had received treatment with rituximab. The first group of patients received lenalidomide 25 mg per day on days 1–21 of a 28-day cycle (29 patients), whereas the subsequent group received lenalidomide at a starting dose of 5 mg per day with the same schedule and dose escalation in increments of 5 mg per day every one to two weeks to a maximum dose of 25 mg per day (16 patients).

The most common adverse events were fatigue, which was observed in 37 patients (83%), and tumor flare reactions, which occurred in 26 patients (58%). Hematologic adverse events, including thrombocytopenia, neutropenia, and anemia, also were prevalent. Febrile neutropenia, however, was reported only in 66 patients (15%). Other nonhematologic treatment-related adverse events included constipation, rash, diarrhea, and infections. Two patients (5%) developed tumor lysis syndrome, both at the 25 mg dose; one had Rai stage III bulky disease and the other had stage IV bulky disease (bulky adenopathy as defined as any single lymph node mass measuring 5 cm in any single dimension).

**M.D. Anderson Cancer Center Study**

In a phase II study conducted at the M.D. Anderson Cancer Center (MDACC), 44 patients with relapsed or refractory CLL were treated with lenalidomide at a starting dose of 10 mg per day with dose escalation in increments of 5 mg every 28 days up to 25 mg per day (Ferrajoli et al., 2008). The median age was 64 years (range 49–86 years), and 20 patients (45%) had advanced-stage disease. Heavily pretreated patients have a worse prognosis (Sturm et al., 2003) and, in comparison to the RPCI study, MDACC enrolled more heavily pretreated patients with a median of five prior therapies (range 1–15). However, patients with fludarabine-refractory disease also have a worse prognosis (Sturm et al., 2003), and fewer patients in this study had fludarabine-refractory disease (n = 12, 27%) than in the RPCI study.

Three hundred thirty-three courses (defined as one month of treatment given to one patient) of lenalidomide therapy were given to all 44 patients, and adverse events were reported in terms of the number of courses affected. As expected, the most commonly observed adverse event was myelosuppression. Specifically, grade 3–4 neutropenia and thrombocytopenia occurred in 131 (41%) and 51 (15%) courses, respectively, whereas anemia was less common; grade 3–4 anemia was reported in 99 courses (3%). Nonhematologic adverse events were mostly mild to moderate in severity. Fatigue was reported in 75 courses (23%). Similarly, diarrhea was observed in 50 courses (15%) and rash occurred in 43 courses (13%). Tumor flare reaction was reported as grade 1–2 in 31 of 333 courses and grade 3–4 tumor flare reactions requiring opioids in 2 of 333 courses. The incidence of tumor flare reactions appeared to be greater in patients with lymph nodes larger than 5 cm than in those with smaller lymph nodes (53% and 15%, respectively), which could suggest that—like tumor lysis syndrome—tumor flare reactions may be associated with a larger tumor burden in the lymph nodes (Cheson, 2009). The fact that tumor lysis syndrome was not observed, although many patients had large tumor volumes, may be explained by the dose escalation of lenalidomide during the study. The rate of severe infections (6% of courses) was not unexpectedly high compared with other studies in refractory patients (Perkins, Flynn, Howard, & Byrd, 2002) given that the patients were severely immunocompromised as a
result of prior treatments and that no antibiotic prophylaxis was given during the study. One patient who was receiving concomitant erythropoietin developed a deep-vein thrombosis (Ferrajoli et al., 2008).

Lenalidomide in Previously Untreated Chronic Lymphocytic Leukemia

Princess Margaret Hospital Study

Preliminary data on lenalidomide in previously untreated, symptomatic patients with CLL were reported from a phase II study conducted at the Princess Margaret Hospital (PMH) in Toronto, Ontario, Canada (Chen et al., 2008). In the PMH study, the starting dose of lenalidomide initially was 10 mg per day and was escalated in 5 mg increments to a target dose of 25 mg per day on days 1–21 of a 28-day cycle. However, severe toxicity in the first two patients (tumor lysis syndrome requiring dialysis and fatal neutropenia from sepsis) led the investigators to modify the starting and target dose to 2.5 mg per day and 10 mg per day on days 1–21, respectively. In addition, the rate at which the dose was escalated was reduced (2.5 mg in cycle 1, 5 mg in cycle 2, 10 mg in cycle 3, etc.), the duration of tumor lysis syndrome prophylaxis with allopurinol was extended to a minimum of three cycles, and the frequency of monitoring for tumor lysis syndrome was increased. A total of 25 patients were treated with the amended protocol. Median age was 60 years (range 33–78 years), and 10 patients (40%) had advanced-stage disease.

Of the 23 patients who received at least one cycle and were evaluable for toxicity, grade 3–4 neutropenia occurred in 10 patients (43%), and 4 patients (17%) developed febrile neutropenia; 3 patients (13%) had grade 3–4 thrombocytopenia. As expected, the three most common nonhematologic adverse events were grade 1–2 tumor flare reactions (n = 18, 78%), fatigue (n = 17, 74%), and rash (n = 11, 48%). The tumor flare reactions presented with painful, enlarged nodes often associated with nasal congestion, coryza, and scalp pruritus. Infections occurred in 10 patients (43%) but were mostly minor, non-neutropenic infections affecting the respiratory tract, sinuses, or skin. No other cases of tumor lysis syndrome were observed in the study.

Of the 17 patients who had completed at least three cycles and were evaluable for response, all had achieved stable disease or better, with an overall response rate of 65% (11 partial responses). Responses were reached at a median of four cycles (range 2–15). Based on the preliminary findings, the investigators concluded that, with a conservative lenalidomide dosing regimen, allopurinol, dosing adjustments, and careful monitoring, tumor lysis syndrome may be minimized in patients with previously untreated CLL. Also, adverse events in the clinical trial, such

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>MONITORING RECOMMENDATION</th>
<th>FREQUENCY OF MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Measure absolute neutrophil count.</td>
<td>Monitor weekly for cycle 1, then every four weeks unless indicated more frequently.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Measure complete blood count.</td>
<td>At 10 mg per day (patients with myelodysplastic syndromes): Monitor weekly for first eight weeks and monthly thereafter. At 25 mg per day (patients with multiple myeloma): Monitor every two weeks for the first three months and monthly thereafter.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NONHEMATOLOGIC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Patient recall of exercise and level of physical activity</td>
<td>Monitor with each follow-up evaluation.</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>Patient reports unusual persistence of symptoms that are not manageable with standard intervention.</td>
<td>Monitor with each follow-up evaluation.</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Monitor for temperature higher than 101.5°F and any flu-like symptoms (e.g., productive cough, upper respiratory symptoms) while receiving therapy.</td>
<td>Monitor with each follow-up evaluation.</td>
</tr>
<tr>
<td>Rash</td>
<td>Examine particularly if tumor flare reaction is present. Monitor grade 1–4 rashes. If grade 4 rash occurs, lenalidomide therapy should be discontinued.</td>
<td>Monitor during physical examination with each follow-up.</td>
</tr>
<tr>
<td>Tumor flare reaction</td>
<td>Monitor for low-grade fever, rash, skin inflammation, sudden onset of tender swelling of lymphadenopathy, and rise in peripheral blood count from baseline.</td>
<td>Monitor during weekly laboratory evaluations and if any symptom-related complaints arise.</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Patients with high tumor burden prior to treatment are at risk. Obtain full metabolic profile, including uric acid, potassium phosphate, creatinine, calcium, and lactate dehydrogenase.</td>
<td>Monitor for at least 24 hours after chemotherapy or until 24 hours after the last therapy of the first cycle for multiagent regimens.</td>
</tr>
</tbody>
</table>

Note. Based on information from Celgene Corporation, 2009; Chanan-Khan et al., 2006.
as tumor flare reactions and myelosuppression, appear to be manageable if patients are monitored and the symptoms are detected and managed early.

### Lenalidomide Dosing in Chronic Lymphocytic Leukemia

Several lenalidomide dosing schedules have been evaluated in patients with relapsed or refractory CLL (Chanan-Khan et al., 2006; Ferrajoli et al., 2008). In the RPCI study, oral lenalidomide was administered at 25 mg per day on days 1–21 of each 28-day cycle, which was later amended because of concerns about tumor lysis syndrome; the starting dose of 5 mg per day then was investigated. In the study by Ferrajoli et al. (2008), patients received continuous lenalidomide 10 mg per day for 28 days escalated to a maximum of 25 mg per day for 28 days compared to the study by Chanan-Khan et al. (2006), which investigated a three week on, one week off schedule similar to the schedule used in multiple myeloma. A phase I study further supported an optimal dosing schedule for lenalidomide in CLL (Wendtner et al., 2009). Wendtner et al. (2009) concluded that the 10 mg per day dose was a safe initiating dose for lenalidomide and that step-wise dose escalation of 5 mg per day every 28 days resulted in a good tolerability profile. A dose-escalation study of lenalidomide in patients with relapsed or refractory CLL is enrolling participants (NCT00419250) and aims to further investigate the efficacy and safety of lenalidomide in CLL and to establish the optimum dose.

### Table 2. Treatment-Related Adverse Events With Lenalidomide in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>RCPI (N = 45)</th>
<th>MDACC (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GRADE 1–2 (%)</td>
<td>GRADE 3–4 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>Anemia</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Tumor flare reaction</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Infection</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Note. Based on information from Chanan-Khan et al., 2006; Ferrajoli et al., 2008.

### Monitoring and Management

Recommendations for the monitoring and management of lenalidomide-related adverse events have been developed for myelodysplastic syndromes and multiple myeloma (Celgene Corporation, 2009; Giagounidis et al., 2008; NCCN, 2008; Palumbo et al., 2008), but no guidelines are available specifically for CLL. The following guidelines are based on the authors’ clinical experience with lenalidomide in CLL at RPCI and the literature.

#### Neutropenia

Lenalidomide is associated with significant neutropenia. In the RCPI study, 70% of patients with CLL developed grade 3–4 neutropenia during lenalidomide therapy (Chanan-Khan et al., 2006). However, lower rates of febrile neutropenia have been observed, with only six (15%) episodes observed in the RCPI study and consistent rates of 3% reported in two other studies (Badoux, Wierda, et al., 2009; Wendtner et al., 2009). The rates of febrile neutropenia are not significantly higher than the 19% observed among heavily pretreated patients with fludarabine-refractory disease (Perkins et al., 2002).

In patients with myelodysplastic syndromes treated with a lenalidomide starting dose of 10 mg per day, median time to onset of grade 3–4 neutropenia was 42 days (range 14–411 days), and the median time to documented recovery was 22 days (range 5–224 days) (List et al., 2006). Guidelines for the management of neutropenia in patients with myelodysplastic syndromes and multiple myeloma receiving lenalidomide therapy are described in detail in the FDA-approved prescribing information for lenalidomide (Celgene Corporation, 2009); weekly monitoring of complete blood counts are recommended for the first eight weeks of therapy and at least monthly thereafter for patients with myelodysplastic syndromes. For patients with multiple myeloma, complete blood counts are recommended every two weeks for the first 12 weeks of therapy and at least monthly thereafter. Depending on the levels of absolute neutrophil counts, patients may require dose interruption or dose reduction.

At RPCI, management of lenalidomide-associated severe neutropenia in patients with CLL generally consists of delaying treatment until the neutropenia resolves to at least grade 2 in severity (see Table 3). Lenalidomide therapy then is resumed, and growth factor support with a granulocyte-colony-stimulating factor may be used at the discretion of the prescriber.

#### Thrombocytopenia

Treatment with lenalidomide is associated with significant thrombocytopenia. In the RCPI study, 45% of patients had grade 3–4 thrombocytopenia (Chanan-Khan et al., 2006). However, of the 29 patients with thrombocytopenia at baseline, 18 (62%) had improvements in thrombocytopenia after the first treatment cycle and 11 (38%) had worsening of thrombocytopenia. The authors observed no bleeding episodes, and only one patient required platelet transfusion because of a platelet count lower than 10,000/mcl.

Thrombocytopenia may be monitored by measuring platelet counts regularly. Patients with myelodysplastic syndromes treated
Table 3. Treatment Recommendations for Adverse Events With Lenalidomide in Patients With Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>TREATMENT RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>For grade 3–4 with fever, delay lenalidomide until neutropenia resolves to grade 2. Resume lenalidomide at the same dose with granulocyte–colony-stimulating factor support if needed.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>With severe thrombocytopenia, interrupt lenalidomide and provide platelet transfusion. Lenalidomide can be resumed at a lower dose once platelet counts have recovered.</td>
</tr>
<tr>
<td><strong>NONHEMATOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>No dose interruption or reduction is required.</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>Loperamide or psyllium fiber</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Antibiotics for bacterial or fungal infections; immunoglobulin infusions for patients with repeated infections</td>
</tr>
<tr>
<td>Rash</td>
<td>For grade 1–2 rash, over-the-counter steroids, topical hydrocortisone, and antihistamines such as diphenhydramine (25 mg every six hours) or hydroxyzine (10 mg every six hours) can be used to manage symptoms. Lenalidomide interruption or discontinuation should be considered in the event of grade 3 or 4 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or suspicion of Stevens-Johnson syndrome or toxic epidermal necrolysis. Treatment should not be resumed following discontinuation for the reactions.</td>
</tr>
<tr>
<td>Tumor flare reaction</td>
<td>Treat with nonsteroidal anti-inflammatory drugs (ibuprofen 400 mg orally every six hours for the duration of the reaction) or a short, six-day course of oral methylprednisolone opioids. Administer opioids (e.g., morphine sulfate) for pain control as necessary. No dose interruption or reduction is required.</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Use aggressive hydration and diuresis. Hospitalize, monitor closely, and take appropriate precautions. Interrupt lenalidomide until symptoms resolve and then resume lenalidomide at the same dose.</td>
</tr>
</tbody>
</table>

Note. Based on information from Celgene Corporation, 2009; Chanan-Khan & Cheson, 2008; Chanan-Khan et al., 2006; Coiffier et al., 2008.

with a starting dose of 10 mg per day should be monitored weekly for the first eight weeks and monthly thereafter (Celgene Corporation, 2009). For patients with multiple myeloma treated with a starting dose of 25 mg per day, blood counts should be monitored every two weeks for the first three months and monthly thereafter (Celgene Corporation, 2009). Severe thrombocytopenia may require treatment interruption and, in some cases, platelet transfusion. In general, lenalidomide therapy may be resumed at a lower dose after platelet counts have recovered.

**Tumor Flare Reaction**

Presenting symptoms of tumor flare reactions include sudden onset of painful enlargement of the lymph nodes or spleen that is sometimes associated with low-grade fever, rash, and bone pain (Chanan-Khan et al., 2006; Ferrajoli et al., 2008). Some patients experience an increase in white blood cells (Chanan-Khan et al., 2006). In the PMH study, patients with tumor flare reactions presented with painful, enlarged nodes often associated with nasal congestion, runny nose, and itchy scalp (Chen et al., 2008). Most of the symptoms resolved spontaneously, although eight patients required steroids on at least one occasion with prompt resolution. In the authors’ experience, onset of tumor flare reactions usually is within 24 hours of the first dose and lasts for a median of 14 days; except for two patients, flare reactions were noted only in the first cycle (Chanan-Khan et al., 2006). Based on the authors’ clinical experience, tumor flare reactions may occur upon restarting treatment after a rest period and may be related to the rebound lymphocytosis that has been observed during treatment breaks with lenalidomide (Chen et al., 2008).

Patients experiencing tumor flare reactions can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen 400 mg orally every six hours for the duration of the reaction (Chanan-Khan et al., 2006) or a short, six-day course of oral methylprednisolone opioids. Administer opioids (e.g., morphine sulfate) for pain control as necessary. No dose interruption or reduction is required. The authors found that low-dose steroids (prednisone 10–20 mg per day) appear to decrease the severity—but not the incidence—of tumor flare reactions (Chanan-Khan & Cheson, 2008; Chanan-Khan et al., 2006). In a retrospective analysis of 45 patients with tumor flare reactions, no patient discontinued or required dose modification of lenalidomide because of tumor flare reactions (Sher et al., 2009).

**Tumor Lysis Syndrome**

Tumor lysis syndrome is a group of metabolic disruptions that can occur as a consequence of the rapid and massive cell killing in response to effective treatment options such as purine analogs, monoclonal antibodies, and immunomodulatory drugs, including lenalidomide (Cheson, 2009). The first patient enrolled in the RPCI study presented after initiating treatment with fever, and the second patient presented with shortness of breath, peripheral edema, generalized weakness, sweating, fever, and tachycardia; both occurred on day 9 of cycle 1 (Chanan-Khan et al., 2006). For both patients, laboratory workup showed hyperuricemia, hyperphosphatemia, uremia,
and either renal failure or worsening serum creatinine levels. Although not present in the two patients, hyperkalemia and hypocalcemia also have been associated with tumor lysis syndrome and are characteristic of the syndrome regardless of selected therapy (Byrd et al., 2005).

Patients experiencing tumor lysis syndrome should be hospitalized as indicated and treated with aggressive hydration and diuresis, with allopurinol or rasburicase added to manage hyperuricemia (Goiffier, Altman, Pui, Younes, & Cairo, 2008). The lenalidomide dose should be interrupted until tumor lysis syndrome resolves. After resolution, lenalidomide can be resumed with prophylaxis (allopurinol 300 mg for 14 days, starting 3 days prior to resuming lenalidomide therapy). Close monitoring is warranted, particularly at treatment initiation and for several days after a dose escalation. Close monitoring includes comprehensive analysis of metabolic profile, including uric acid, phosphate, potassium, calcium, and lactate dehydrogenase levels. In the RPCI study, outpatients were monitored three times daily. If patients showed signs of laboratory changes, they were immediately hydrated and monitored for additional changes in laboratory parameters.

**Fatigue**

In the RPCI study, 13 patients (29%) had fatigue at baseline and 73% had grade 1–2 fatigue during the study. Of the four patients with grade 3–4 fatigue, two had resolution within two months of initiating therapy, whereas the other two continued to experience fatigue while taking lenalidomide (Chan-an-Khan et al., 2006). No correlation existed between fatigue and tumor flare reactions. Of note, grade 3–4 fatigue does not warrant treatment interruption or reduction in the dose of lenalidomide. Patients should be advised to report fatigue symptoms so that specific interventions may be addressed. For more information, visit www.ons.org/Research/PEP/Fatigue.

**Gastrointestinal Complications**

The most common type of gastrointestinal complication observed during lenalidomide therapy is diarrhea. In the authors’ experience, antidiarrheal agents such as loperamide (Imodium®, McNeil PPC, Inc.) usually are effective in managing diarrhea. Some patients derive benefit from psyllium fiber; for more information, visit www.ons.org/Research/PEP/Diarrhea.

**Rash**

Rash in patients with CLL frequently presents as a generalized erythematous rash that is pruritic, macular, and raised. In the authors’ experience, rash can be a direct effect of treatment lenalidomide and can be associated with flare reactions. Grade 1 or 2 rash occurred in 13% of patients in the MDACC study (Ferrajoli et al., 2008). Rash following lenalidomide administration also has been observed in other indications (Celgene Corporation, 2009). At RPCI, grade 1–2 rash is managed most often with over-the-counter steroids, topical hydrocortisone, and antihistamines, such as diphenhydramine (25 mg every six hours) or hydroxyzine (10 mg every six hours). Lenalidomide interruption or discontinuation should be considered for grade 3–4 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, or exfoliative or bullous rash or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected; lenalidomide should not be resumed following discontinuation for those reactions (Celgene Corporation, 2009).

**Infectious Complications**

Patients with CLL, particularly those with relapsed or refractory disease, are immunocompromised because of the effects of the disease and previous treatment, which reduce the amount of infection-fighting white blood cells in the blood and pose a risk for infection (Dearden, 2008). In a study investigating infectious complications in fludarabine refractory CLL, Perkins et al. (2002) found that the rate of serious infections (those requiring hospitalization and IV antibiotics) was high (89%) and resulted in mortality in 48% of patients (Perkins et al., 2002). Patients who had been treated previously have higher rates of infection compared with those who have not been treated previously (58% versus 34%; p < 0.001) (Anaissie et al., 1998). Previous chemotherapy (reported as an answer to a yes or no question), treatment with three or more previous therapies, and prior fludarabine treatment all are predictive of infection (Anaissie et al., 1998; Tam et al., 2004). Other factors increasing risk for infection include Rai stage III or IV, elevated serum creatinine levels (Anaissie et al., 1998), older age (older than 60 years), time from diagnosis to treatment of more than three years, performance status of 2 or higher, and baseline absolute neutrophil count lower than 2 x 10^9/L (Tam et al., 2004). Antibiotics may be used to treat infections caused by bacteria or fungi in patients with CLL. For CLL therapies associated with immunosuppressive adverse events, IV immunoglobulin can be given to manage repetitive infectious complications. However, in lenalidomide therapy, treatment is associated with a significant increase in immunoglobulin levels; immunoglobulin G levels were normalized in 7 of 12 (58%) patients with hypogammaglobulinemia (Badoux, Reuben, et al., 2009).

**Venous Thromboembolism**

The risk of venous thromboembolic events, including deep-vein thrombosis and pulmonary embolism, was increased in patients with multiple myeloma treated with combination lenalidomide and dexamethasone (Celgene Corporation, 2009; Dimopoulos et al., 2007). Patients should be advised to be observant for signs and symptoms of thromboembolism, such as shortness of breath, chest pain, or swelling in the arms or legs. Whether prophylactic anticoagulation with weight-based warfarin reduced the risk for venous thromboembolic events in patients with CLL or multiple myeloma treated with thalidomide–based combination therapies was investigated at RPCI (Miller et al., 2006). Patients weighing 70 kg or less received 1 mg per...
day warfarin, and patients weighing more than 70 kg received 2 mg per day warfarin. Of the 68 patients enrolled, 4 patients (6%) developed a venous thromboembolic event, which was significantly lower compared with previously reported rates of 26%–27% (Miller et al., 2006). The consensus statement from the International Myeloma Foundation’s Nurses Leadership Board recommends that patients should be monitored for signs and symptoms of venous thromboembolic events and receive prophylaxis by individual patient-, disease-, and treatment-related risk factors according to the following criteria: aspirin for those at low risk and low-molecular weight heparin or full-dose warfarin for those at higher risk (Rome, Doss, Miller, Westphal, & IMF Nurse Leadership Board 2008). NCCN guidelines (2009) state that thalidomide or lenalidomide plus dexamethasone are associated with higher risk of venous thromboembolic events and that medical (nonsurgical) patients at higher risk for venous thromboembolic events should receive prophylaxis of low-molecular weight heparin, fondaparinux, or unfractionated heparin. The authors recommend that patients with CLL treated with lenalidomide or lenalidomide-based therapies should receive some form of prophylaxis.

Other Considerations

Lenalidomide generally is not associated with nephrotoxicity, and no cases of treatment-related nephrotoxicity were reported in studies of patients with CLL (Chanan-Khan et al., 2006; Chen et al., 2008; Ferrajoli et al., 2008). However, as elimination of lenalidomide relies primarily on the kidneys, drug concentrations may be increased in patients with renal dysfunction; therefore, patients may have a greater risk of developing adverse events. As a result, older adult patients who may be more prone to renal impairment should have their renal function monitored throughout lenalidomide treatment so that appropriate dose selection can be made.

Conclusions

The most common treatment-related adverse events observed in CLL patients are myelosuppression, fatigue, rash, gastrointestinal and infectious complications, and tumor flare reactions. Severe neutropenia and thrombocytopenia are frequent events, but with adequate monitoring and management, few patients develop fever or infections or require transfusions. Regular monitoring of blood cell counts is recommended. Another important adverse event noted in patients with CLL is tumor flare reactions with initial signs of a sudden onset of painful enlargement of the lymph nodes or spleen, with or without low-grade fever, rash, and bone pain. Patients experiencing tumor flare reactions may be treated with NSAIDs or a short course of corticosteroids; some patients may require opioids for pain control. Of note, treatment delays and dose reductions are unnecessary for tumor flare reactions. Tumor lysis syndrome is a possible and potentially serious adverse event observed in patients with CLL treated with lenalidomide. Signs of tumor lysis syndrome may include fever, shortness of breath, peripheral edema, generalized weakness, sweating, fever, and tachycardia. Laboratory analyses may show hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, uremia, and either renal failure or worsening serum creatinine. Management of tumor lysis syndrome requires treatment interruption until resolution. Other adverse effects, such as fatigue, pruritus, and gastrointestinal complications, do not require treatment interruptions or dose reductions and may be managed with conventional interventions in most patients. With proper monitoring and management of the toxicities, lenalidomide can be safely administered to patients with CLL with minimal dose interruptions or reductions.

The authors take full responsibility for the content of the article but thank Marianna Shafarenko, PhD, supported by Celgene Corporation, for medical writing support. Miller has received honoraria from Celgene Corporation, and Chanan-Khan is a consultant for and has received research funds from Celgene Corporation. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff.

Author Contact: Kena C. Miller, RN, MSN, FNP, can be reached at kena.miller@roswellpark.org, with copy to editor at CJONEditor@ons.org.

References


