Mantle-cell lymphoma (MCL), which accounts for approximately 6% of new non–Hodgkin lymphoma diagnoses, is a rare and often aggressive cancer. MCL is most often diagnosed in older white adults (typically patients are in their mid-60s) and is usually in advanced stages. Splenomegaly and lymph node enlargement are typically present, in addition to bone marrow, liver, and gastrointestinal tract involvement.

Although genetic abnormalities (ie, translocations of chromosomes 11 and 14) and the overexpression of cyclin D1 are characteristic of MCL, their clinical and prognostic implications remain unclear. A recent analysis of 62 cases of MCL demonstrated that other disease features, particularly blastoid (vs classical) morphology and the presence of TP53 gene mutations, are significantly correlated with poor clinical outcomes.

MCL is an uncommon diagnosis in the United States. A study using Surveillance, Epidemiology and End Results (SEER) registry data collected between 1992 and 2001 documented an incidence rate of 0.51 per 100,000 person-years. In this analysis, patients diagnosed with MCL were more likely to be white and male. An 8% annual increase in the incidence of MCL was noted during the 10-year time frame over which data were collected, but researchers hypothesized that changes in diagnostic practices explained this trend.

The clinical course of MCL can be indolent or moderately aggressive at diagnosis. Over time, however, the disease invariably becomes clinically aggressive and refractory to cytotoxic chemotherapy. Data reported in 1995 suggest that patients with MCL have the worst long-term survival among patients with all B-cell lymphoma subtypes, with a median survival of approximately 3 years. In a more recent series of patients with MCL, this estimate has increased to approximately 5 years, possibly as a result of the use of anthracycline-containing treatment regimens, stem-cell transplantation, advances in supportive care, and the general improvement of life span.

Although assessments of the cost burden associated with MCL are few, the results of a recent cost-effectiveness analysis that was conducted using US payer data showed that total per-patient costs for patients with MCL exceeded $100,000. This study, which compared the combination of bendamustine and rituximab (BR) with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in treatment-naïve patients with MCL, calculated average per-patient costs of $115,191 and $100,261 for BR and R-CHOP, respectively.

Until recently, bortezomib (Velcade) was the only drug approved by the US Food and Drug Administration (FDA) for the treatment of patients with MCL, specifically those who have received at least 1 previous therapy. In clinical practice, combinations of chemotherapy with anti-CD20 monoclonal antibody therapy, high-dose chemotherapy followed by stem-cell transplant, and radioimmunotherapy are viable options for the treatment of patients with MCL.

Novel options that are being investigated in MCL clinical trials include cytotoxic agents (bendamustine, cladribine); monoclonal antibodies (rituximab); mTOR inhibitors (temsirolimus, which is approved in Europe for MCL); cyclin-dependent kinase inhibitors (flavopiridol); histone deacetylase inhibitors; B-cell leukemia/lymphoma-2 inhibitors; Bruton’s tyrosine kinase inhibitors; and immunotoxins.

Revlimid a New Treatment Option for Patients with MCL

In June 2013, the FDA approved the immunomodulatory agent lenalidomide (Revlimid; Celgene Corporation) for the treatment of patients with MCL whose disease has relapsed or progressed after 2 previous therapies, one of which included bortezomib.

The approval of lenalidomide for MCL was based on the demonstration of efficacy (overall response rate [ORR] and duration of response) in a phase 2 multi-center clinical trial of 134 heavily pretreated patients with MCL. Data from this trial, known as the MCL-001 EMERGE study, were presented at the annual meeting of the American Society of Hematology in December 2012 and were published in September 2013.
In a recent interview regarding his experience in this phase 2 trial of lenalidomide in patients with MCL, Andre Goy, MD, MS, Chairman and Director, and Chief of Lymphoma, John Theurer Cancer Center, Hackensack, NJ, stated, “What was very important was the duration of response….Here, the median duration of response was more than 16 months…regardless of the number of prior therapies; bulky, high tumor load; [and] prior high-dose chemotherapy refractory to the last therapy or refractory to bortezomib.”

Lenalidomide is also approved for use in combination with dexamethasone in patients with multiple myeloma (MM) who have received at least 1 previous therapy, and in patients with transfusion-dependent anemia resulting from low- or intermediate-1–risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities.15

**Mechanism of Action**

As an analog of thalidomide, lenalidomide has immunomodulatory, antangiogenic, and antineoplastic properties. In vitro, the drug inhibits cell proliferation and induces programmed cell death of specific hematopoietic tumor cells, including MM, MCL, and MDS associated with a deletion 5q abnormality. Lenalidomide also has immunomodulatory properties: it activates T-cells and natural killer cells, increases the number of natural killer T-cells, and inhibits proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, by monocytes.15

**Phase 2 Clinical Trial: MCL-001 EMERGE**

In the phase 2 multicenter MCL-001 EMERGE trial, Goy and colleagues enrolled 134 patients with MCL who had been treated with multiple therapies, including rituximab, cyclophosphamide, and anthracycline.13 All patients had MCL that had relapsed or had progressed within 12 months of therapy with bortezomib or whose disease was refractory to bortezomib. Lenalidomide was given as a single agent at a dose of 25 mg daily administered on days 1 to 21 of a 28-day cycle until disease progression, unacceptable toxicity, or voluntary withdrawal.13 The lenalidomide dose was 10 mg once daily for 21 days every 28 days for patients with a creatinine clearance between 30 mL/min and 59 mL/min.15

The primary end points of the MCL-001 EMERGE study were ORR and duration of response.13 Duration of response was defined as the time from initial response to documented disease progression.13 Secondary end points included complete response (CR), progression-free survival, time to progression, overall survival, and safety.13

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Independent central review (N = 134)</th>
<th>Investigator assessed (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>7.5</td>
<td>16</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>16.6 (95% CI, 7.7-26.7)</td>
<td>18.5 (95% CI, 12.8-26.7)</td>
</tr>
<tr>
<td>Median time to response, mo</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Median progression-free survival, mo</td>
<td>3.6-5.6</td>
<td>3.5-6.8</td>
</tr>
<tr>
<td>Median overall survival, mo</td>
<td>19.0 (95% CI, 12.5-23.9)</td>
<td>19 (95% CI, 12.5-23.9)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; MCL, mantle-cell lymphoma. Source: Revlimid (lenalidomide) capsules prescribing information; 2013.

The efficacy parameters were assessed by investigators, as well as by an independent central review committee.13

**Patient Population**

The median age of patients enrolled in the phase 2 study of lenalidomide was 67 years.13 The majority of patients in this trial were male (81%) and white (96%), with advanced (stage III/IV) MCL (93%).13,15 Of these patients, 78% had received 3 or more previous treatments (median, 4; range, 2-10).13

**Efficacy**

The phase 2 study demonstrated that lenalidomide monotherapy is active and safe in patients with MCL whose disease has relapsed or progressed after bortezomib therapy or whose disease was refractory to bortezomib. According to independent central review, the ORR was 28% (7.5% CR) and the median duration of response was 16.6 months. According to investigators, the ORR was 32% (16% CR) and the median duration of response was 18.5 months. Table 1 includes these data, as well as secondary end point data, from the phase 2 study of lenalidomide.13

**Adverse Events**

More than half of the patients (58%) received 3 or more cycles of lenalidomide in this trial.13 The median duration of therapy was 95 days (range, 1-1022 days) and the average dose of lenalidomide was 20 mg daily.13 Of the patients with MCL, 38% required a dose reduction of lenalidomide.13

The most common grade 3 or 4 adverse events reported in the study were neutropenia (43%), thrombocytopenia (27%), anemia (11%), pneumonia (8%), and fatigue (7%).13 Other adverse events of any grade included
A total of 19% of the patients in this study discontinued lenalidomide therapy because of adverse events.13

Dosing and Administration

For patients with MCL whose disease relapsed or progressed after bortezomib therapy or was refractory to bortezomib, the recommended dose and schedule for lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.15 Lenalidomide should be taken at approximately the same time each day, either with or without food.15 The FDA approval of lenalidomide for the treatment of patients with MCL also included an approval of a new 20-mg capsule strength of this agent.15

Table 2 summarizes lenalidomide dose modification guidelines for patients with grade 3 or 4 neutropenia or thrombocytopenia, or with other grade 3 or 4 toxicities that are believed to be drug-related.15

Table 3 summarizes starting dose adjustments for patients with MCL and renal insufficiency.15

<table>
<thead>
<tr>
<th>Renal impairment level</th>
<th>Creatinine clearance (Cockcroft-Gault)</th>
<th>Lenalidomide adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate impairment</td>
<td>30-60 mL/min</td>
<td>10 mg every 24 hrs</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>&lt;30 mL/min not requiring dialysis</td>
<td>15 mg every 48 hrs</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>&lt;30 mL/min requiring dialysis</td>
<td>5 mg once daily</td>
</tr>
</tbody>
</table>

MCL indicates mantle-cell lymphoma.
Source: Revlimid (lenalidomide) capsules prescribing information; 2013.

Hematologic Toxicity

In the phase 2 trial of lenalidomide in MCL, grade 3 or 4 neutropenia and grade 3 or 4 thrombocytopenia were reported in 43% and 28% of patients, respectively.13 Patients with MCL who take lenalidomide should have their complete blood count (CBC) monitored.15 CBC tests are recommended weekly for the first cycle (28 days), every 2 weeks during cycles 2 to 4, and then monthly while receiving lenalidomide therapy.15
Venous Thromboembolism

Some patients with MCL who received lenalidomide experienced venous thromboembolic events, typically deep venous thrombosis and pulmonary embolism. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide can minimize the risk of venous thromboembolism.

Allergic Reactions

Lenalidomide has been associated with angioedema and serious dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Such reactions can be fatal. Physicians should consider interruption or discontinuation of lenalidomide for grade 2 to 3 skin reactions. Lenalidomide must be permanently discontinued if angioedema, grade 4 rash, exfoliative or bullous rash occur, or if Stevens-Johnson syndrome occurs or toxic epidermal necrolysis is suspected. Lenalidomide should not be given to any patient who experienced a grade 4 rash while receiving thalidomide.

Tumor Lysis Syndrome

Fatalities secondary to tumor lysis syndrome have been documented in patients taking lenalidomide. Because patients with high tumor burden before treatment are at risk for tumor lysis syndrome, healthcare professionals should monitor these patients closely and take appropriate precautions.

Tumor Flare Reaction

Patients with MCL taking lenalidomide should be monitored for tumor flare reaction, which is characterized by lymph node swelling, low-grade fever, pain, and rash. Of patients in the MCL trial, 10% experienced grade 1 or grade 2 tumor flare reaction in the first cycle of lenalidomide treatment. One of these patients developed tumor flare reaction again in cycle 11. If grades 1 and 2 tumor flare reaction occur, lenalidomide can be continued without interruption or modification, at the physician’s discretion. Corticosteroids, nonsteroidal anti-inflammatory drugs, and/or narcotic analgesics can be used for symptom management. Patients who experience more severe tumor flare reaction (grade 3 or 4) should not receive lenalidomide treatment until the tumor flare reaction resolves to grade 1 or less.

Second Primary Malignancies

Patients taking lenalidomide should be monitored for the development of second malignancies. In the MCL trial, 3 patients (2%) developed invasive secondary malignancies.

Conclusion

Lenalidomide, the first oral drug approved for the treatment of patients with MCL, has demonstrated efficacy with manageable toxicities in heavily pretreated patients whose disease has relapsed or progressed after bortezomib or is refractory to bortezomib. Lenalidomide joins bortezomib as the only 2 FDA-approved agents currently available for this rare and often aggressive form of B-cell lymphoma. Because it is not cytotoxic, lenalidomide may offer clinical value when combined with other treatments for MCL. Current clinical trials are evaluating the use of lenalidomide in combination with rituximab, bendamustine, and/or bortezomib in patients with MCL for use as first- or second-line treatment.

References

12. Goy A, Sinha R, Williams ME, et al. Phase II multicenter study of single-agent lenalidomide in subjects with mantle cell lymphoma who relapsed or progressed after or were refractory to bortezomib: the MCL-001 “EMERGE” study. Presented at the American Society of Hematology annual meeting; December 8-11, 2012; Atlanta, GA.