Revlimid (Lenalidomide) First Drug Approved for Post-Transplant Maintenance Therapy in Multiple Myeloma

By Lisa A. Raedler, PhD, RPh, Medical Writer

Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure. According to the American Cancer Society, more than 30,280 new cases of multiple myeloma will be diagnosed in 2017, and 12,590 deaths will be attributed to the disease. In the past 20 years, mortality rates associated with multiple myeloma have declined. Novel therapies, as well as improvements in autologous hematopoietic stem-cell transplantation (HSCT) procedures and supportive care, have contributed to extended survival for patients with this malignancy.

"Lenalidomide maintenance therapy, which has been shown to increase progression-free survival following autologous stem cell transplant in clinical trials, can be considered a standard of care for these patients."

New drugs and novel combination regimens for multiple myeloma reflect the improved understanding of the bone marrow microenvironment and disease biology. Immunomodulatory drugs (IMiDs) and proteasome inhibitors are the cornerstones of initial induction therapy for multiple myeloma based on their ability to deepen responses and extend survival. Yet, despite significant strides in the safety of drug therapy and autologous HSCT, multiple myeloma remains incurable. Progression-free survival (PFS) after induction therapy, followed by autologous HSCT rarely exceeds 3 years. Consequently, for more than a decade, the concept of using maintenance therapy after autologous HSCT has been explored.

Maintenance therapy with interferon, prednisone, dexamethasone, and thalidomide, with or without bortezomib (Velcade), has been evaluated in large clinical trials, with mixed results. The lack of a consistent overall survival (OS) benefit, combined with challenging toxicity profiles, have precluded these maintenance strategies from becoming the standard of care.

Lenalidomide Approved as Maintenance Therapy

On February 22, 2017, the US Food and Drug Administration (FDA) approved lenalidomide (Revlimid; Celgene), an oral IMiD, for maintenance therapy after autologous HSCT in patients with multiple myeloma. This expanded indication was based on the safety and efficacy results from 2 randomized, placebo-controlled studies that demonstrated PFS advantages for lenalidomide maintenance therapy. With this approval, lenalidomide became the first and only drug to be approved by the FDA as maintenance treatment for patients with multiple myeloma after autologous HSCT.

"Autologous stem cell transplant after induction therapy is part of the continuum of care for transplant-eligible multiple myeloma patients. However, most patients will still see their disease recur or progress after this treatment," said Philip McCarthy, MD, Director, Blood and Marrow Transplant Center, Department of Medicine at Roswell Park Cancer Institute. "Lenalidomide maintenance therapy, which has been shown to increase progression-free survival following autologous stem cell transplant in clinical trials, can be considered a standard of care for these patients."

The FDA initially approved lenalidomide in 2005 for the treatment of patients with transfusion-dependent anemia because of low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q abnormality, with or without additional cytogenetic abnormalities.

In 2006, the FDA approved lenalidomide in combination with dexamethasone for patients with multiple myeloma who received at least 1 previous therapy. In 2015, the FDA approved lenalidomide as first-line treatment for patients with newly diagnosed multiple myeloma.

In addition to multiple myeloma and myelodysplastic syndromes, in 2013 lenalidomide was also approved by the FDA for the treatment of patients with mantle-cell
lymphoma whose disease relapsed or progressed after 2 previous therapies, including bortezomib.8

Dosing and Administration

In patients with multiple myeloma who have undergone autologous HSCT and whose bone marrow has recovered adequately (absolute neutrophil counts ≥1000/mcL and/or platelet counts ≥75,000/mcL), lenalidomide maintenance therapy should be initiated at a dose of 10 mg once daily continuously until disease progression or until unacceptable toxicity.8

After approximately 3 months, if tolerated, the dose of lenalidomide can be increased to 15 mg once daily. Subsequent dose increases or decreases of lenalidomide should be based on individual patient tolerance to treatment.8

Pivotal Clinical Trials

The efficacy of maintenance therapy with lenalidomide after autologous HSCT was demonstrated in 2 multicenter, randomized, double-blind, placebo-controlled studies, CALGB 100104 (Study 1) and IFM 2005-02 (Study 2).8-10

Study 1 included patients aged 18 to 70 years who had undergone induction therapy, followed by autologous HSCT. Within 90 to 100 days after transplant, 460 patients with at least stable disease were randomized to receive maintenance therapy with lenalidomide or placebo.8

Study 2 enrolled patients with multiple myeloma aged <65 years at the time of diagnosis who had undergone induction therapy followed by autologous HSCT, and who achieved at least stable disease at the time of hematologic recovery. Overall, 614 patients were randomized to receive lenalidomide or placebo maintenance therapy within 6 months of undergoing transplantation.8

In both studies, the lenalidomide maintenance dosage was 10 mg once daily. After 3 months, the dose could be increased to 15 mg once daily if no dose-limiting toxicity was observed.8 Treatment continued until disease progression or until patient withdrawal. Dose escalation to 15 mg once daily occurred in 58% of patients in Study 1 and in 60% of patients in Study 2. Patients in the placebo arm of Study 1 were allowed to receive lenalidomide maintenance therapy before disease progression, but patients in Study 2 were not.8

PFS was the primary end point in both studies. Neither study was powered to demonstrate an OS difference.8-10 In both studies, the median PFS was significantly longer with lenalidomide compared with placebo (Table).8

In Study 1, the median PFS was 33.9 months with lenalidomide versus 19.0 months with placebo. In Study 2, the median PFS was 41.2 months with lenalidomide versus 23.0 months with placebo (Table). After longer follow-up, updated PFS analyses for both studies continued to show a PFS advantage for lenalidomide compared with placebo.8

Adverse Events

Adverse reactions that occurred in more than 20% of patients who received lenalidomide in Study 1 and in Study 2 included neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhea, rash, and fatigue.8

Grade 3 or 4 adverse reactions that occurred in more than 20% of patients who received lenalidomide included neutropenia, thrombocytopenia, and leukopenia. In general, the rates of adverse reactions were the highest during the first 6 months of treatment with lenalidomide.8

Contraindications

Because lenalidomide is structurally similar to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women.8

Lenalidomide is also contraindicated in patients with a hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.8

Use in Specific Populations

Lenalidomide can cause embryo-fetal harm when administered to a pregnant woman and is contraindicated during pregnancy.8

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Table Study 1 and Study 2: Lenalidomide versus Placebo After Transplantation in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenalidomide (N = 231)</td>
<td>Placebo (N = 229)</td>
</tr>
<tr>
<td>PFS at unblinding5</td>
<td>33.9 (95% CI, 24.0-44.1)</td>
<td>19.0 (95% CI, 16.2-21.8)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.38 (95% CI, 0.27-0.54)</td>
<td>0.50 (95% CI, 0.39-0.64)</td>
</tr>
<tr>
<td>PFS at updated analysis: March 1, 20156</td>
<td>68.6 (95% CI, 52.8-NE)</td>
<td>22.5 (95% CI, 18.8-30.0)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.38 (95% CI, 0.28-0.50)</td>
<td>0.53 (95% CI, 0.44-0.64)</td>
</tr>
</tbody>
</table>

5Intent-to-treat patient population.
6PFS at time of unblinding for Study 2 was based on assessment by an independent review committee; all other PFS analyses were based on investigator assessment. CI indicates confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Source: Revlimid (lenalidomide) capsules prescribing information; February 2017.
Women should be advised not to breast-feed during treatment with lenalidomide.\(^8\)

Grade 3 or 4 adverse events were higher in patients aged ≥65 years who received lenalidomide than in younger patients.

The starting dose of lenalidomide should be adjusted based on creatinine clearance value and in patients undergoing dialysis.

**Select Warnings and Precautions**

The prescribing information for lenalidomide contains a boxed warning stating that lenalidomide therapy is associated with a risk for embryo-fetal toxicity if used during pregnancy, risk for hematologic toxicity, the need for antithrombotic prophylaxis to mitigate the risk for venous and arterial thromboembolism, and the drug’s availability only through a Risk Evaluation and Mitigation Strategy program.\(^8\)

Women must avoid pregnancy 4 weeks before taking lenalidomide, while taking lenalidomide, and for at least 4 weeks after completing lenalidomide therapy.\(^8\)

Men must use a condom during sexual contact with women of reproductive potential during lenalidomide therapy and for 28 days after discontinuing lenalidomide, even if a successful vasectomy has been performed. Men taking lenalidomide should not donate sperm.\(^8\)

Patients must not donate blood during lenalidomide therapy and for 1 month after.\(^8\)

Patients taking lenalidomide should be monitored for hematologic toxicities. In clinical trials, grade 3 or 4 neutropenia was reported in up to 59% of patients who received lenalidomide maintenance therapy, and grade 3 or 4 thrombocytopenia was observed in up to 38% of patients.\(^8\)

Venous and arterial thromboembolic events have occurred in patients who received lenalidomide. Thromboprophylaxis is recommended.\(^8\)

Second primary malignancies have been reported in patients with multiple myeloma who received lenalidomide. Patients should be monitored appropriately.\(^8\)

Combining lenalidomide and a PD-I or PD-L1 inhibitor plus dexamethasone is not recommended in patients with multiple myeloma, except in clinical trials.

Liver failure, including fatal cases, have been reported in patients who received lenalidomide plus dexamethasone. Liver function tests should be assessed periodically.\(^8\)

Angioedema and serious dermatologic reactions have been reported with lenalidomide and can be fatal. Lenalidomide capsules contain lactose; the risks and benefits of lenalidomide therapy should be evaluated in patients with lactose intolerance.\(^8\)

Tumor lysis syndrome (TLS), including fatalities, can occur with lenalidomide. Patients who are at risk for TLS (eg, those with a high tumor burden before treatment) should be monitored closely.\(^8\)

Patients with mantle-cell lymphoma should be monitored for tumor flare reactions. Lenalidomide has been associated with early mortality risk in patients with mantle-cell lymphoma.

Impaired stem-cell mobilization has been reported after >4 cycles of lenalidomide therapy. Patients who are candidates for autologous HSCT should be referred to a transplant center early for stem-cell collection.

Hypothyroidism and hyperthyroidism have been reported with lenalidomide and should be assessed during therapy.\(^8\)

**Conclusion**

The FDA approval of lenalidomide, an oral IMiD, for maintenance therapy in patients with multiple myeloma who have undergone autologous HSCT provides a new long-term treatment for this patient population. Two large clinical trials demonstrated significant PFS benefits, as well as an acceptable safety profile, in these patients.\(^1\)

**References**