Revlimid (Lenalidomide) Receives New Indication for Multiple Myeloma as Maintenance Therapy After Transplantation

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.

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.

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, lenalidomide is also approved by the FDA for the treatment of patients with mantle-cell lymphoma that relapsed or progressed after 2 previous therapies, including bortezomib.

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. 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.

Lenalidomide Distribution

Lenalidomide is available through select specialty pharmacies and pharmacy networks, including Accredo Specialty Pharmacy, ACRO Pharmaceutical Services, Advanced Care Scripts, Aetna Specialty Pharmacy, Amber Pharmacy, Avella Specialty Pharmacy, Axium Healthcare Pharmacy, Biologics, BioPlus Specialty Pharmacy, BrioVaRx, CareMed Specialty Pharmacy, CIGNA Specialty...
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 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

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

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

Selected Warnings and Precautions

Box warning. The prescribing information for lenalidomide contains a box 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.9

Embryo-fetal toxicity. Women must avoid pregnancy 4 weeks before taking lenalidomide, while taking lenalidomide, and for at least 4 weeks after completing lenalidomide therapy.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>
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<tbody>
<tr>
<td></td>
<td>Lenalidomide (N = 329)</td>
<td>Placebo (N = 329)</td>
</tr>
<tr>
<td>PFS at unblinding*</td>
<td>33.9 (95% CI, 16.2-25.8)</td>
<td>19.0 (95% CI, 16.2-25.8)</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>
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</table>

PFS at updated analysis: March 1, 2015*

| Hazard ratio | 0.38 (95% CI, 0.28-0.50) | 0.53 (95% CI, 0.44-0.64) |

OS at updated analysis: February 1, 2016

| Hazard ratio | 0.59 (95% CI, 0.44-0.78) | 0.90 (95% CI, 0.72-1.13) |

*Intent-to-treat patient population.

**PFS 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.
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 discontinuing lenalidomide.8

**Hematologic toxicity.** 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

Thromboprophylaxis is recommended.8

**Second primary malignancies.** Second primary malignancies have been reported in patients with multiple myeloma who received lenalidomide. Patients should be monitored closely.8

**Hepatotoxicity.** Liver failure, including fatal cases, has been reported in patients who received lenalidomide. Liver function tests should be assessed periodically.8

**Hypersensitivity reactions.** Angioedema and serious dermatologic reactions have been reported with lenalidomide. Lenalidomide capsules contain lactose; the risks and benefits of lenalidomide therapy should be evaluated in patients with lactose intolerance.8

**Tumor lysis syndrome (TLS).** TLS 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

**Thyroid disorders.** Hypothyroidism and hyperthyroidism have been reported with lenalidomide therapy. Thyroid function should be assessed before and during therapy.8

**Use in Specific Populations**

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

**Lactation.** Women should be advised not to breastfeed during treatment with lenalidomide.8

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

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

**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.8

**References**