Pomalyst (Pomalidomide) Received a New Indication for Patients with Relapsed and/or Refractory Multiple Myeloma

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Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure.[1,2] According to the American Cancer Society, more than 26,800 new cases of multiple myeloma were diagnosed in 2015, and 11,240 deaths were attributed to the disease.[3]

Representing approximately 1% of all cancers, multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma.[4] The incidence of multiple myeloma is higher among men than in women.[1] Individuals aged ≥65 years, those with a family history of the disease, and those with a history of monoclonal gammopathy of undetermined significance are at increased risk for multiple myeloma.[1] Several common complications of multiple myeloma include bone pain, kidney dysfunction, bone loss, impaired immunity, and anemia.[5]

Although the overall incidence of multiple myeloma continues to increase, the mortality rates associated with this malignancy have declined during the past 20 years.[1,6] Specifically, the advent of novel therapy options for multiple myeloma, as well as improvements in high-dose therapy and supportive care have contributed to extended survival for patients with multiple myeloma.[6]

New anticancer drugs and novel combinations have emerged in part because of improved understanding of the bone marrow microenvironment and the biology of multiple myeloma.[7] Immune modulators and proteasome inhibitors now represent the cornerstones of initial treatment for multiple myeloma based on their ability to enhance the overall response rates and survival.[2,7]

Because novel agents have had a considerable impact on the US healthcare, understanding their relative cost-effectiveness is important for ensuring efficient use. Overall, 2 recent evaluations of the economics of new agents in multiple myeloma resulted in similar conclusions.[8,9]

Based on claims data from more than 2600 patients with multiple myeloma, one study showed that the 1-year cost of bortezomib-based therapy was similar to the cost of older drug combinations (approximately $112,000 each), whereas the costs of thalidomide- and lenalidomide-based regimens were significantly higher (approximately $130,500 and $159,200, respectively) than older combinations.[8] In addition, patients taking thalidomide and lenalidomide had higher out-of-pocket costs because of Medicare Part D coverage gaps.[8]

The second study modeled the cost-effectiveness of novel agents combined with melphalan and prednisone in patients with newly diagnosed multiple myeloma who were ineligible for a transplant.[9] The researchers concluded that adding bortezomib to melphalan and prednisone was more cost-effective than adding thalidomide or lenalidomide to the same drug combination.[9]

Despite strides in the treatment of multiple myeloma, patients will experience disease relapse after initial treatment and several lines of therapy are typically required.[10]

Specifically, resistance to bortezomib and to lenalidomide is being observed with increasing frequency; therefore, there remains a marked need for additional therapeutic options for patients with double-refractory multiple myeloma.[11]

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Pomalidomide Approved for Relapsed and/or Refractory Multiple Myeloma

On April 23, 2015, the US Food and Drug Administration (FDA) approved a new indication for pomalidomide (Pomalyst; Celgene), for use in combination with low-dose dexamethasone, for the treatment of patients with relapsed and/or refractory multiple myeloma who have received at least 2 previous lines of therapy, including lenalidomide and a proteasome inhibitor, and whose disease progressed during or within 60 days of completing the last therapy.[12]

The drug labeling now includes data regarding additional efficacy end points, including progression-free survival and overall survival.[12] This update was based on the final analysis of data from the MM-003 clinical trial, an international phase 3 study comparing the combination of pomalidomide and low-dose dexamethasone versus high-dose dexamethasone in patients with multiple my-

eloma who had received at least 2 previous regimens.[12-14]

Pomalidomide, an oral agent, initially received accelerated approval by the FDA in 2013 for patients with multiple myeloma after 2 previous therapies, including lenalidomide and bortezomib, whose disease progressed during or within 60 days of completing the last therapy.[15] That initial approval was based on results of the MM-002 study, an open-label, phase 2 clinical trial.[12,16] In this study, the overall response rate with pomalidomide and low-dose dexamethasone was 29% versus 7% with pomalidomide alone.[14,15]

Mechanism of Action

Pomalidomide is an immunomodulatory agent with multiple actions.[14] Pomalidomide inhibits the proliferation and induces the apoptosis of hematopoietic tumor cells based on in vitro cellular assays. Pomalidomide also hinders the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergizes with dexamethasone in lenalidomide-sensitive and -resistant cell lines to induce apoptosis. Pomalidomide enhances T-cell– and natural killer cell–mediated immunity, and blocks the production of proinflammatory cytokines, such as tumor necrosis factor–α and interleukin-6.[14]

Dosing and Administration

The recommended dose of pomalidomide is 4 mg daily taken orally on days 1 to 21 of each 28-day cycle until disease progression. Pomalidomide should be taken at least 2 hours before or after a meal. It can be swallowed with water. Patients should not break, chew, or open the capsules.[14]

Pomalidomide is supplied in 4 capsule strengths—1 mg, 2 mg, 3 mg, and 4 mg.[14]

Table Efficacy Results from the MM-003 Clinical Trial in Patients with Relapsed and/or Refractory Multiple Myeloma

Efficacy end point	Pomalidomide plus low-dose dexamethasone (N = 302)	High-dose dexamethasone (N = 153)
Progression-free survival, mo (median)	3.6 (95% CI, 3.0-4.6)	1.8 (95% CI, 1.6-2.1)
Hazard ratio	0.45 (95% CI, 0.35-0.59)	
P value (2-sided)	<.001	
Overall survival, mo (median)	12.4 (95% CI, 10.4-15.3)	8.0 (95% CI, 6.9-9.0)
Hazard ratio	0.70 (95% CI, 0.54-0.92)	
P value (2-sided)	.009	
Overall response rate, %	23.5	3.9
Complete response, %	0.3	0
Very good partial response, %	2.6	0.7
Partial response, %	20.5	3.3

CI indicates confidence interval.
Source: Pomalyst (pomalidomide) capsules prescribing information; April 2015.

MM-003 Clinical Trial

The new indication for pomalidomide for use in relapsed and/or refractory multiple myeloma was based on results from the phase 3, multicenter, randomized, open-label MM-003 clinical trial that enrolled patients with relapsed and/or refractory multiple myeloma who had received at least 2 previous lines of therapy.[13,14]

A total of 455 patients (median age, 64 years) enrolled in the MM-003 study.[14] Patients in the pomalidomide plus dexamethasone arm received 4 mg of pomalidomide orally on days 1 through 21 of each 28-day cycle and 40 mg of dexamethasone once daily on days 1, 8, 15, and 22 during each 28-day cycle. Patients in the high-dose dexamethasone arm received 40 mg of dexamethasone once daily on days 1 through 4, 9 through 12, and 17 through 20 during each 28-day cycle. In both study arms, patients aged >75 years started treatment with 20 mg of dexamethasone using the same schedule. Treatment continued until disease progression.[14]

The majority (75%) of patients had disease that was refractory to lenalidomide and to bortezomib. Overall, 71% of patients had undergone stem-cell transplantation.[14] In addition, patients had received a median of 5 previous therapies (range, 2-14).[13,14]

The median progression-free survival was significantly higher in the pomalidomide plus low-dose dexamethasone arm compared with high-dose dexamethasone (3.6 vs 1.8 months, respectively; **Table**).[14]

The final overall survival analysis also showed a significant benefit for pomalidomide plus low-dose dexamethasone compared with high-dose dexamethasone (12.4 vs 8.0 months, respectively; hazard ratio [HR], 0.70; *P* = .009), even though 53% of patients in the high-dose dexamethasone arm subsequently received pomalidomide.[14]

According to the study investigators, the combination of pomalidomide plus low-dose dexamethasone significantly improved progression-free survival, overall survival, and overall response rate compared with high-dose dexamethasone in patients with relapsed and/or refractory disease, including patients with disease refractory to bortezomib and to lenalidomide.[13]

Adverse Events

The safety data were evaluated in 450 patients who received treatment with pomalidomide plus low-dose

dexamethasone (N = 300) or high-dose dexamethasone (N = 150).[14]

Overall, 67% of patients taking the pomalidomide combination interrupted pomalidomide therapy after a median of 4.1 weeks. In addition, 27% of patients required a dose reduction of pomalidomide after a median of 4.5 weeks, and 8% of patients discontinued pomalidomide therapy because of adverse events.[14]

The most common adverse reactions (all grades) observed with pomalidomide plus low-dose dexamethasone at a rate of >10% overall and at least 5% higher than high-dose dexamethasone in the MM-003 study included neutropenia (51% vs 21%, respectively), upper respiratory tract infection (31% vs 13%), dyspnea (25% vs 17%), constipation (22% vs 15%), cough (20% vs 10%), pneumonia (19% vs 13%), peripheral neuropathy (17% vs 12%), peripheral edema (17% vs 11%), muscle spasms (15% vs 7%), decreased appetite (13% vs 8%), and leukopenia (13% vs 5%).[14]

The most common severe (grade ≥3) adverse reactions among patients taking pomalidomide plus low-dose dexamethasone included neutropenia (48%), thrombocytopenia (22%), pneumonia (16%), febrile neutropenia (9%), leukopenia (9%), and fatigue or asthenia (9%).[14]

Contraindications

Pomalidomide is contraindicated in pregnant women, because of the risk for severe birth defects and embryofetal death.[14]

Warnings and Precautions

Boxed warning. The safety information for pomalidomide includes a boxed warning regarding the risk for embryofetal toxicity if used during pregnancy, its availability only through a Risk Evaluation and Mitigation Strategy (REMS) program, and the need for antithrombotic prophylaxis to mitigate the risk for venous and arterial thromboembolism.[14]

Embryo-fetal toxicity. Pomalidomide is an analog of thalidomide, a known human teratogen that causes severe birth defects and embryo-fetal death.[14]

Females of reproductive potential. Women must avoid becoming pregnant while taking pomalidomide, and for at least 4 weeks after completing therapy.[14]

Males. Because pomalidomide is present in the semen of men receiving the drug, men must use a condom during sexual contact with females of reproductive age while taking pomalidomide, and for 28 days after discontinuing therapy. Men taking pomalidomide must not donate sperm.[14]

Blood donation. Because donated blood may be given to a pregnant woman, patients must not donate blood during treatment with pomalidomide, and for 1 month after discontinuing therapy.[14]

REMS program. Because of the embryo-fetal risk associated with pomalidomide therapy, pomalidomide is available only through a REMS program.

Thromboembolism. Venous and arterial thromboembolic events have occurred in patients receiving pomalidomide. Thromboprophylaxis is recommended.[14]

Hematologic toxicity. Patients taking pomalidomide should be monitored for hematologic toxicities, particularly neutropenia. Complete blood counts should be performed weekly for the first 8 weeks and monthly thereafter. Pomalidomide dose interruption and/or modification may be necessary.[14]

Hepatotoxicity. Liver failure, including fatal cases, and elevated levels of alanine aminotransferase and bilirubin have been noted in patients receiving pomalidomide. Liver function tests should be assessed monthly. If liver enzymes are elevated, pomalidomide should be stopped.[14]

Hypersensitivity reactions. Angioedema and severe dermatologic reactions have been reported with pomalidomide. The drug should be permanently discontinued if angioedema, skin exfoliation, bullae, or other severe dermatologic reactions occur.[14]

Dizziness and confusion. Patients should avoid situations in which dizziness or confusion may be problematic.[14]

Neuropathy. Neuropathy, including peripheral neuropathy, has been reported in patients receiving pomalidomide plus low-dose dexamethasone.[14]

Second primary malignancies. Acute myelogenous leukemia has been reported in patients with tumor types other than multiple myeloma who were receiving investigational pomalidomide.[14]

Tumor lysis syndrome (TLS). TLS can occur in patients receiving pomalidomide. Patients who are at risk for TLS should be monitored closely.[14]

Use in Specific Populations

Pregnancy. Pomalidomide is contraindicated during pregnancy.[14]

Lactation. There are no data regarding the presence of pomalidomide in human milk.[14]

People of reproductive potential. Females of reproductive potential must avoid becoming pregnant while taking pomalidomide, and for at least 4 weeks after completing pomalidomide therapy. Men must always use a condom during any sexual contact with females of reproductive potential while taking pomalidomide, and for up to 28 days after discontinuing pomalidomide. Men taking pomalidomide must not donate sperm.[14]

Pediatric use. No data are available about the safety and effectiveness of pomalidomide in pediatric patients.[14]

Geriatric use. No differences in the effectiveness of

pomalidomide were observed between older and younger patients taking pomalidomide in clinical trials. In these studies, patients aged >65 years were more likely to have pneumonia compared with patients aged ≤65 years.[14]

Renal impairment. Pomalidomide should not be used in patients with serum creatinine levels >3 mg/dL.[14]

Hepatic impairment. Pomalidomide should not be used in patients with serum bilirubin levels >2 mg/dL or whose liver enzyme levels exceed 3 times the upper limit of normal.[14]

Pomalidomide is now indicated for use in patients with relapsed and/or refractory multiple myeloma based on updated data showing improved progression-free survival and overall survival in patients receiving pomalidomide plus low-dose dexamethasone.

Conclusion

Pomalidomide is now indicated for use in patients with relapsed and/or refractory multiple myeloma based on updated data showing improved progression-free survival and overall survival in the MM-003 clinical trial in patients receiving pomalidomide plus low-dose dexamethasone compared with high-dose dexamethasone.

Investigators continue to evaluate the clinical activity of pomalidomide monotherapy and pomalidomide plus dexamethasone-based combinations in patients with multiple myeloma, as well as in other hematologic malignancies.[17] ■

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