Pomalyst (Pomalidomide): A New Third-Generation Immunomodulatory Drug for Relapsed and/or Refractory Multiple Myeloma

By Lynne Lederman, PhD, Medical Writer

Multiple myeloma (MM) is characterized by the clonal expansion of malignant plasma cells that proliferate in the bone marrow, which typically produce large amounts of an abnormal immunoglobulin-like protein.\(^1,2\) The etiology of MM is unknown, but is associated with exposure to particular chemicals or to radiation and with being overweight or obese.\(^3,4\) MM is often preceded by monoclonal gammopathy of undetermined significance, an asymptomatic plasma-cell disorder, which may progress through asymptomatic smoldering MM before becoming symptomatic MM.\(^2,5\)

The Burden of Myeloma

Approximately 10% to 15% of all hematologic malignancies and 20% of deaths from hematologic cancers result from MM.\(^2,5\) The American Cancer Society estimates that in 2013, 22,350 Americans will be newly diagnosed with MM and 10,710 Americans will die from the disease.\(^4\) This represents an increase in the number of cases but not of deaths compared with in 2012.\(^4,6\) The frequent signs and symptoms of MM include fatigue, bone pain, osteolytic bone lesions, and/or compression fractures.\(^7\) Myeloma-related organ or tissue damage (eg, hypercalcemia, anemia, renal dysfunction, or bone lesions) is required to establish a diagnosis of symptomatic MM.\(^1\)

The median survival for patients with MM has increased from <1 year before the introduction of alkylating agents in the 1960s, to almost 2 years after the development of high-dose chemotherapy and autologous stem-cell transplant in the 1980s.\(^2,8\)

Since approximately 2000, the development of novel, targeted therapies, including the immunomodulatory drugs (IMiDs) thalidomide (Thalomid) and lenalidomide (Revlimid) and the proteasome inhibitor bortezomib (Velcade), have increased survival to a median of 5.4 years.\(^8,9\) However, a recent analysis shows that it is primarily patients aged >65 years who have benefited the most from novel agents, and there remains a need for additional new therapies for younger patients and to effect a cure.\(^9\)

The Challenge of Relapsed, Refractory Myeloma

Although MM may be initially sensitive to treatment, it remains incurable.\(^2,8\) MM almost always eventually relapses, the duration of remission shortens with each successive therapy,\(^10\) and it becomes more resistant to chemotherapy over time,\(^2\) indicating a need for additional salvage therapies. The 2012 US Food and Drug Administration (FDA) accelerated approval of carfilzomib (Kyprolis), which is indicated for the treatment of relapsed and/or refractory MM, provides another treatment option,\(^11\) as does the continuing development of other antmyeloma agents.\(^12\)

Pomalidomide: A Third-Generation Immunomodulatory Drug

On February 8, 2013, the FDA approved pomalidomide (Pomalyst; Celgene), the most recent IMiD, for the treatment of patients with MM who have received at least 2 previous therapies, including lenalidomide and bortezomib, and have demonstrated disease progression within 60 days of the completion of the last therapy.\(^11\) The FDA accelerated the approval of pomalidomide based on a phase 2 clinical trial.

Value-Based Cancer Care discussed the FDA approval of pomalidomide with Paul G. Richardson, MD, Clinical Director, Jerome Lipper Center for Multiple Myeloma, and Professor of Medicine, Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, who conducts clinical trials of pomalidomide, among other antmyeloma therapies.\(^13-16\)

“I want to applaud the FDA. They moved very quickly with it, and they have been very proactive in meeting unmet medical needs,” said Dr Richardson. “Pomalidomide absolutely fills an unmet need for patients,” he emphasized. Of note, the approval is based on response rate, and any clinical benefit, such as increased survival or improvement of symptoms, has not been confirmed.\(^17\)

Pomalidomide is an analog of thalidomide and is the third agent in the immunomodulatory class that includes thalidomide and lenalidomide.\(^12\) Although thalidomide, particularly when combined with dexamethasone, is very active against MM, it is associated with dose-limiting adverse effects, including somnolence, constipation, neuropathy, and thromboembolic events. Derivatives of thalidomide, including lenalidomide and pomalidomide,
have been developed that have their own safety and efficacy profiles.

Like lenalidomide, pomalidomide is thought to act directly on myeloma cell adhesion and by decreasing factors that are required for myeloma cell survival, leading to cell death, and indirectly by modulating cells in the bone marrow microenvironment. According to Dr Richardi, for patients with MM whose disease is resistant to lenalidomide and to bortezomib, the orally available and generally well-tolerated pomalidomide provides a major step forward.

**Phase 2 Registration Trial Results**

The FDA accelerated the approval of pomalidomide based on the results of an open-label, randomized phase 2 clinical trial that included 221 patients with relapsed MM refractory to the last therapy and who had received at least lenalidomide and bortezomib. Response rate was the primary objective. The patients were randomly assigned to receive pomalidomide plus low-dose dexamethasone (pomalidomide 4 mg once daily for 21 of 28 days plus low-dose dexamethasone 40 mg daily for patients aged ≤75 years or 20 mg daily for patients aged ≥75 years on days 1, 8, 15, and 22 of each 28-day cycle; N = 113) or pomalidomide alone (N = 108) until disease progression. Patients in the pomalidomide alone arm were allowed to add low-dose dexamethasone on disease progression.

For the efficacy analysis, 221 patients were evaluable for response; 219 patients were evaluable for safety, including 112 patients who received pomalidomide plus low-dose dexamethasone and 107 patients who received pomalidomide alone. Of those 107 patients, 61 had low-dose dexamethasone added during the treatment period.

The overall response rate was 7.4% in the pomalidomide arm and 29.2% in the arm receiving pomalidomide plus low-dose dexamethasone (Table 1). The duration of response was 7.4 months in the arm receiving pomalidomide plus low-dose dexamethasone, and it was not reached in the pomalidomide-alone arm.

**Dosing**

Pomalidomide is administered orally at a starting dose of 4 mg once daily on days 1 to 21 of each 28-day cycle. The cycles are repeated until disease progression. Pomalidomide capsules should be swallowed whole, with water, at least 2 hours before or 2 hours after a meal, and should not be taken with food.

Dexamethasone may be used in combination with pomalidomide, for example, at the doses administered in the registration phase 2 trial.

**Important Safety Information for Pomalidomide**

The prescribing information for pomalidomide contains a Boxed Warning about serious adverse events that may occur with this drug, including:

- Pomalidomide is contraindicated in pregnancy, because it is an analog of the teratogen thalidomide, which can cause life-threatening birth defects. For women of childbearing age, pregnancy must be excluded before treatment, and pregnancy must be prevented during treatment by the use of 2 reliable contraceptive methods.
- Deep-vein thrombosis (DVT) and pulmonary embolism (PE) can occur in patients with MM who are treated with pomalidomide.
- Pomalidomide is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Although patients in the pomalidomide registration trial received mandated prophylaxis or antithrombotic agents (either aspirin [81%], heparin [21%], warfarin [16%], or clopidogrel [3%]), 3% of patients developed venous thromboembolism. Therefore, the risk for DVT and PE should be evaluated for each patient to decide on the use of prophylaxis against thrombotic events.

Patients treated with pomalidomide should be monitored for hematologic toxicities, particularly neutropenia, which was the most frequent grade 3 or 4 adverse event reported (43% of patients). The pomalidomide dose may be modified depending on the degree of neu-
tropenia or thrombocytopenia. Other clinically significant adverse reactions and drug interactions are listed in Table 2.

**Restricted Distribution Program**

Because of the potential for embryonic and fetal toxicities, pomalidomide will only be available in the United States through a restricted distribution program called the Pomalyst REMS program.

The Pomalyst REMS program requires that all patients be enrolled and agree to comply with its requirements before they can receive pomalidomide, both as an initial prescription and at each subsequent prescription refill. In addition, only certified prescribers can prescribe pomalidomide, and only certified pharmacies can dispense pomalidomide.

**Conclusions**

The FDA approval of pomalidomide adds a new treatment option for patients with myeloma whose disease has relapsed after treatment with other drugs or has developed resistance to the other options.

In his discussion with Value-Based Cancer Care, Dr Richardson said that “pomalidomide is the most potent immunomodulatory drug we have tested so far. Its efficacy is reflected by the fact that it is able to overcome resistance to both lenalidomide and bortezomib. Because it is able to achieve a response in about a third of patients who are both resistant to lenalidomide and bortezomib, it has provided a major step forward and an excellent choice after lenalidomide and bortezomib fail.” Pomalidomide works very well with dexamethasone, as currently indicated, and it also “partners well” with other agents, including bortezomib or carfilzomib. Combination trials with pomalidomide are ongoing, and the results for efficacy and safety are promising.

**References**