Farydak (Panobinostat): First HDAC Inhibitor Approved for Patients with Relapsed Multiple Myeloma

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Multiple myeloma, also referred to as 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 will be diagnosed in 2015, and 11,240 deaths will be attributed to this disease.[3]

Multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma, representing approximately 1% of all cancer cases.[4] Although the overall incidence of myeloma in the United States has increased nearly 1% annually since 1975, the mortality rates associated with this disease have declined during the past 2 decades.[1]

Multiple myeloma occurs more often in men than in women. Middle-aged and older individuals and those with a family history of multiple myeloma or with a personal history of monoclonal gammopathy of undetermined significance are at an increased risk for multiple myeloma.[1]

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Complications associated with multiple myeloma include bone pain, kidney dysfunction, bone loss, impaired immunity, and anemia.[5] Based on one study, the annual US costs attributed to metastatic bone disease, including myeloma, were an estimated $12.6 billion.[6] The median cost for patients with metastatic bone disease was $75,329 annually compared with $31,382 annually for cancers that are not associated with metastatic bone disease. The regression-adjusted incremental costs for patients with multiple myeloma were $57,720 compared with $44,442 across all cancer types (P <.001).[6]

The treatment of patients with multiple myeloma has evolved substantially in recent years. The introduction of novel drugs with new mechanisms of action, including immune modulators and proteasome inhibitors, as well as a better understanding of the bone marrow microenvironment, have led to new combination therapies and new anticancer drugs.[7] In fact, the use of novel agents for first-line treatment of myeloma has improved outcomes, including overall responses, for patients with relapsed or refractory myeloma.[7] Nevertheless, despite strides in the treatment of patients with multiple myeloma, there remains a marked need for additional therapeutic options and approaches for this patient population.[8]

Current therapies for multiple myeloma include chemotherapy, corticosteroids, immune modulators, proteasome inhibitors, radiation, stem-cell transplantation, and supportive care.[1]

Because patients with multiple myeloma will experience disease relapse after initial treatment, multiple lines of therapy may be required. The therapeutic considerations include the duration of response to previous treatment, as well as the toxicity profiles of specific treatments and patient-specific factors.

Panobinostat Receives FDA Approval

On February 23, 2015, the US Food and Drug Administration (FDA) approved panobinostat (Farydak; Novartis Pharmaceuticals), an orally administered inhibitor of histone deacetylase (HDAC), for the treatment of patients with multiple myeloma who have received at least 2 previous regimens, including bortezomib and an immunomodulatory agent.[9,10]

Panobinostat was approved under the FDA's accelerated approval program, which allows approval of a drug to treat a serious or life-threatening disease based on clinical data showing the drug has an effect on a surrogate end point likely to predict clinical benefit. The FDA approval was based on progression-free survival data. An improvement in survival or in disease-related symptoms has not yet been demonstrated for panobinostat, and confirmatory clinical trials must be conducted to verify and describe the drug's clinical benefit.[9]

According to Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, "Farydak has a new mechanism of action that distinguishes it from prior drugs approved to treat multiple myeloma, making it a

potentially attractive candidate agent. Farydak's approval is particularly important because it has been shown to slow the progression of multiple myeloma."[9]

Panobinostat's labeling includes a boxed warning to alert patients and healthcare professionals about the risk for severe diarrhea and severe and fatal cardiac events, including cardiac ischemic events, arrhythmias, and electrocardiogram changes associated with the use of panobinostat.[10] Consequently, panobinostat was approved with a Risk Evaluation and Mitigation Strategy program, which includes a communication plan to inform and educate healthcare professionals about these risks.[9,10]

Mechanism of Action

Panobinostat blocks the enzymatic activity of HDACs at nanomolar concentrations. HDACs are responsible for removing acetyl groups from the lysine residues of histones and some nonhistone proteins. HDAC inhibition increases the acetylation of histone proteins, which causes the relaxation of chromatin and leads to transcriptional activation. In vitro, panobinostat-mediated accumulation of acetylated histones and other proteins results in cell-cycle arrest and/or apoptosis of some transformed cells. Overall, panobinostat is more cytotoxic in tumor cells than in normal cells.[10]

Dosing and Administration

Panobinostat is available as an oral capsule and is administered in combination with bortezomib and dexamethasone. The recommended starting dose of panobinostat is 20 mg once every other day for 3 doses weekly in weeks 1 and 2 of each 21-day cycle for up to 8 cycles. Continued treatment with panobinostat for an additional 8 cycles can be considered for patients with clinical benefit who do not experience unresolved severe or medically significant toxicity. The total treatment duration with panobinostat should not exceed 16 cycles (ie, 48 weeks).[10]

When panobinostat is used in combination with bortezomib and dexamethasone, the recommended dose of bortezomib is 1.3 mg/m^2, administered via injection, and the recommended dose of dexamethasone is 20 mg taken orally on a full stomach.[10] **Table 1** and **Table 2** summarize the recommended dosing schedule for the 3 drugs.

Panobinostat capsules should be swallowed whole with a cup of water, and can be administered with or without food.[10]

PANORAMA-1: Phase 3 Clinical Trial

The efficacy and safety of panobinostat combined with bortezomib and dexamethasone were evaluated in the PANORAMA-1 study, a double-blind, placebo-controlled, phase 3 multicenter clinical trial that enrolled 768 patients with relapsed multiple myeloma who had received 1 to 3 previous lines of therapy.[10,11]

Table 1 Recommended Dosing for Panobinostat plus Bortezomib and Dexamethasone in Cycles 1 to 8

Cycles 1-8 (21-day cycles)	Week 1 days							Week 2 days							Week 3
Panobinostat	1		3		5			8		10		12			Rest period
Bortezomib	1			4				8			11				Rest period
Dexamethasone	1	2		4	5			8	9		11	12			Rest period

Source: Farydak (panobinostat) capsules prescribing information; February 2015.

Table 2 Recommended Dosing for Panobinostat plus Bortezomib and Dexamethasone in Cycles 9 to 16

Cycles 9-16 (21-day cycles)	Week 1 days							Week 2 days							Week 3
Panobinostat	1		3		5			8		10		12			Rest period
Bortezomib	1							8							Rest period
Dexamethasone	1	2						8	9						Rest period

Source: Farydak (panobinostat) capsules prescribing information; February 2015.

Patients in PANORAMA-1 were randomized to receive panobinostat in combination with bortezomib and dexamethasone (N = 387; panobinostat arm) or placebo in combination with bortezomib and dexamethasone (N = 381; control arm).[10,11] Patients were stratified by previous bortezomib use and by the number of previous lines of therapy. The clinical trial's primary end point was progression-free survival. The secondary end points included overall survival, overall response rate, time to response, and safety.[11] The median duration of patient follow-up was 29 months in both study arms.[10]

Patient Population

The median age of patients with relapsed multiple myeloma who participated in the PANORAMA-1 clinical trial was 63 years (range, 28-84 years).[10] The majority of patients were male (53%) and Caucasian (65%) with Eastern Cooperative Oncology Group performance status of 0 to 1 (93%).[10] Overall, 57% of patients had undergone stem-cell transplantation.[10] Although the median number of previous therapies was 1, 48% of patients received 2 or 3 previous lines of therapy, which included corticosteroids (90%), melphalan (80%), thalidomide (53%), cyclophosphamide (47%), bortezomib (44%), and lenalidomide (19%).[10]

Efficacy

The FDA approval of panobinostat was based on its efficacy and safety in a prespecified subgroup of 193 pa-

tients who received previous treatment with bortezomib and an immunomodulatory agent; overall, 76% of patients in this subgroup received 2 or more previous lines of therapy.[10] The benefit–risk ratio associated with the panobinostat-containing regimen was greater in this more heavily pretreated patient subset of patients relative to the overall clinical trial population.

The median progression-free survival in this predefined patient subset was 10.6 months (95% confidence interval [CI], 7.6-13.8) in the panobinostat arm versus 5.8 months (95% CI, 4.4-7.1) in the control arm (hazard ratio, 0.52 [95% CI, 0.36-0.76) (**Table 3**)].[10] The overall response rate was 59% in the panobinostat arm versus 41% in the control arm.[10]

Adverse Events

The safety data for the combination of panobinostat with bortezomib and dexamethasone are derived from the PANORAMA-1 clinical trial.[10] In this study, the median duration of exposure to panobinostat was 5 months.[10] Overall, 60% of patients who received the panobinostat-containing regimen experienced a serious adverse event compared with 42% of patients in the control arm.[10]

The most common (≥5%) treatment-emergent serious adverse event reported with panobinostat included pneumonia (18%), diarrhea, (11%), thrombocytopenia (7%), fatigue (6%), and sepsis (6%).[10] Overall, 36% of patients experienced adverse reactions that led to panobinostat discontinuation, including diarrhea, fatigue, and pneumonia.[10]

Deaths occurred in 8% of patients in the panobinostat arm compared with 5% of patients in the control arm[10]; the majority of deaths were attributed to infection and hemorrhage.

Panobinostat has no contraindications.[10]

Drug Interactions

The panobinostat dose should be reduced when coadministered with strong cytochrome (CY) P3A4 inhibitors (eg, ketoconazole).[10]

The concomitant use of panobinostat with strong CYP3A4 inducers (eg, rifampin), sensitive CYP2D6 substrates (eg, metoprolol, venlafaxine), or antiarrhythmic/QT-prolonging drugs should be avoided.[10]

Table 3 Efficacy Results: Adding Panobinostat versus Placebo to Treatment Regimen in Patients Who Received Previous Bortezomib and Dexamethasone

Efficacy variables	Panobinostat, bortezomib, dexamethasone (N = 94)	Placebo, bortezomib, dexamethasone (N = 99)
Progression-free survival		
Median, mo	10.6 (95% CI, 7.6-13.8)	5.8 (95% CI, 4.4-7.1)
Hazard ratio[a]	0.52 (95% CI, 0.36-0.76)	

[a]Hazard ratio obtained from stratified Cox model.
CI indicates confidence interval.
Source: Farydak (panobinostat) capsules prescribing information; February 2015.

Warnings and Precautions

Boxed warning. Panobinostat includes a boxed warning regarding severe diarrhea and cardiac events. Panobinostat therapy should be interrupted and restarted at a reduced dose or discontinued if diarrhea is reported. Severe and fatal cardiac ischemic events, severe arrhythmias, and echocardiogram changes have occurred in patients taking panobinostat. An echocardiogram and electrolyte levels should be obtained at baseline and during treatment as clinically indicated.[10]

Diarrhea. Because diarrhea can occur at any time, hydration status and electrolyte levels should be assessed at baseline and at least weekly during therapy with panobinostat. Treatment should be interrupted if patients report 4 to 6 stools daily.[10]

Cardiac toxicities. Panobinostat should not be prescribed to patients with a history of recent myocardial infarction or unstable angina. Electrocardiographic abnormalities, including ST-segment depression and T-wave abnormalities, were observed more often in patients receiving panobinostat compared with control patients. An electrocardiogram should be conducted at baseline and periodically during treatment. If QT prolongation occurs and does not resolve, panobinostat therapy should be discontinued.[10]

Hemorrhage. Serious and fatal hemorrhage have been observed in patients receiving panobinostat. In PANORAMA-1, 5 patients with relapsed multiple myeloma who received panobinostat and 1 patient in the control arm died as a result of a bleeding event.[10]

Myelosuppression. Myelosuppression, including severe thrombocytopenia, neutropenia, and anemia, has occurred with panobinostat use. Severe neutropenia was reported in 34% of patients receiving panobinostat versus 11% of control patients. Neutropenia required treatment interruption and/or dose modification in 10% of patients who received panobinostat.[10]

Infections. Severe and fatal infections occurred in patients who received panobinostat.[10] Panobinostat treatment should not be given to patients with active infections.[10]

Hepatotoxicity. Patients who received panobinostat experienced hepatic dysfunction, primarily elevations in aminotransferases and total bilirubin levels. Liver function should be monitored at baseline and regularly during treatment. Consider dose adjustments of panobinostat if hepatic dysfunction is observed.[10]

Embryo-fetal risk. Because panobinostat can cause

fetal harm when administered during pregnancy, females of reproductive potential should avoid becoming pregnant while taking panobinostat and should use effective contraception while taking panobinostat. Sexually active men should use condoms while taking panobinostat and for 3 months after the last dose.[10]

Use in Specific Populations

Pregnancy. Women who are pregnant while taking panobinostat should be informed of potential hazards to the fetus.[10]

Nursing mothers. It is not known whether panobinostat is excreted in human milk.[10]

Pediatric use. The safety and efficacy of panobinostat in children have not been established.[10]

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Geriatric use. No overall differences in the efficacy of panobinostat were observed between patients aged ≥65 years and younger patients.[10] Patients aged ≥65 years had a higher incidence of specific adverse events, including death, and were more likely to discontinue treatment as a result of adverse events.[10]

Renal impairment. Dosing adjustments are not necessary for patients with renal impairment.[10]

Hepatic impairment. The starting dose of panobinostat should be reduced in patients with mild or moderate hepatic impairment and should be avoided in severe hepatic impairment.[10]

Conclusions

Panobinostat, a new therapeutic option with a novel mechanism of action, improves progression-free survival when combined with bortezomib and dexamethasone in patients with relapsed multiple myeloma who previously received bortezomib and an immunomodulatory agent.[10,11] Panobinostat is the first HDAC inhibitor approved in the United States for use in this subgroup of patients. Clinical studies are currently under way to evaluate the use of panobinostat in combination with other agents and regimens in the settings of previously untreated patients with multiple myeloma and patients with relapsed multiple myeloma.[12] ■

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