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Commentary

Panobinostat and Multiple Myeloma in 2018

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Disclosures of potential conflicts of interest may be found at the end of this article.

Panobinostat's approval for third-line treatment of multiple myeloma (MM), as Farydak (Novartis, Basel, Switzerland), established an entry for a promising new avenue of treatment. In this commentary, we will review the evolving strategy of using histone deacetylase (HDAC) inhibitors in this disease.

HDAC inhibitors such as vorinostat (Zolinza; Merck, Kenilworth, NJ) and now panobinostat (Farydak) are an important new class of drugs in oncology [1]. By increasing histone acetylation, HDAC inhibition leads to transcriptional activation and other nuclear events. There are several classes of HDACs, and there are also nonhistone substrates of HDACs in the cytoplasm through which HDAC inhibitors have manifold effects. These pleiotropic effects may be key to their efficacy, such as protein degradation via the aggresome, protein-protein interactions, and protein localization.

In MM, preclinical work with proteasome and HDAC inhibitors showed synergistic activity by effects on proteasomal and aggresomal protein degradation systems, leading to accumulation of polyubiquitinated proteins and activation of apoptosis [2, 3]. Proteasome inhibitors such as bortezomib have become a cornerstone of therapy in MM and are widely used in newly diagnosed patients and at time of relapse, leading to significant improvements in overall survival [4]. This set the stage for the clinical development of HDAC inhibitors in MM as combination therapy, beginning with vorinostat, a pan-HDAC inhibitor. Combinations are necessary, because as single agents, HDAC inhibitors alone do not have significant activity in MM. VANTAGE 088 was a phase III trial of vorinostat in combination with bortezomib compared with bortezomib alone in relapsed and/or refractory MM with one to three prior lines of therapy [5]. Although this study showed statistically significant improvement in progression-free survival, the difference of 0.8 months (7.63 vs. 6.83 months) was minimal and not clinically meaningful.

Panobinostat (LBH589) is an oral pan-HDAC inhibitor that is now approved for the treatment of relapsed MM. PANORAMA-1 was a phase III trial comparing panobinostat, bortezomib, and dexamethasone with bortezomib and dexamethasone in a patient population similar to VANTAGE 088 with one to three prior lines of therapy [6]. Patients with disease refractory to bortezomib were excluded. Panobinostat 20 mg was given orally on Monday, Wednesday, and Friday for 2 weeks, and bortezomib was given intravenously on a conventional 21-day schedule on days 1, 4, 8, and 11. The median progression-free survival was significantly longer in the panobinostat arm, 11.99 months, versus 8.08 months in the control arm ($p < .0001$). However, as in the vorinostat study, there was more grade 3–4 diarrhea in the panobinostat arm (25%) than in the control arm (8%). Deaths from causes other than disease progression were also higher in the panobinostat arm (7% vs. 3%). Given some of these concerns, the U.S. Food and Drug Administration (FDA) in November 2014 deferred accelerated approval of panobinostat as second-line therapy.

Panobinostat was later re-evaluated as third-line therapy. In a prespecified subgroup analysis of 193 patients who received prior treatment with both bortezomib and an immunomodulatory drug and who had a median of two prior therapies, the benefit with panobinostat was more apparent. The median progression-free survival was 10.6 months in the panobinostat arm versus 5.8 months in the control arm, and the overall response rate (ORR) was also higher—59% versus 41%, respectively. Given the larger benefit in this more challenging-to-treat patient population, the FDA gave panobinostat accelerated approval in February 2015 for patients who received at least two prior lines of therapy, including bortezomib and an immunomodulatory drug [7]. Based on a similar analysis summarized by Tzogani et al. in this issue, the European Medicines Agency approved panobinostat in August 2015 [8].

Since the approval of panobinostat, the treatment options for relapsed MM have expanded considerably. Several new agents, including the anti-SLAMF7 monoclonal antibody elotuzumab, the oral proteasome inhibitor ixazomib, and the anti-CD38 monoclonal antibody daratumumab are all recently FDA-approved options. In particular, the impressively deep and sustained responses of daratumumab in combination with lenalidomide [9], bortezomib [10], or pomalidomide [11] have become a new standard for second- and third-line treatment. Moreover, the field is moving towards more triplet combinations, such as carfilzomib with lenalidomide and dexamethasone [12]; carfilzomib with pomalidomide and dexamethasone [13]; or pomalidomide, bortezomib, and dexamethasone [14], as additional options for patients. Therefore, although panobinostat has been approved, its role in the treatment paradigm of myeloma continues to be explored and to evolve.

Panobinostat is attractive, given its unique mechanism of action. However, ongoing concerns for panobinostat are diarrhea, as noted above, and cardiac events such as arrhythmias, given the association between panobinostat and QT prolongation. Some of this toxicity, however, could be mitigated by modifications in the dosing of panobinostat and/or the drugs used in combination. In the second phase of the PANORAMA-1 trial, when

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bortezomib was given weekly instead of twice per week, there was a significant improvement in the frequency of diarrhea [15]. Administration of bortezomib subcutaneously, which is now standard practice, instead of intravenously, as done in the trial, may further reduce side effects. PANORAMA-3 (NCT02654990) is an ongoing trial evaluating lower doses of panobinostat with subcutaneous bortezomib and dexamethasone. Panobinostat has also been combined with lenalidomide and dexamethasone in a phase II trial [16]. In this trial, there were no significant gastrointestinal toxicities, and the addition of panobinostat was able to recover responses in lenalidomide-refractory patients, with an ORR of 36% in this population. Other combinations that have been explored with panobinostat include bortezomib, thalidomide, and dexamethasone in the MUK-six trial [17]; carfilzomib [18]; and bortezomib, lenalidomide, and dexamethasone [19].

The benefit of HDAC inhibition may be improved by targeting specific HDACs, as some of the toxicity of panobinostat may reflect its activity across all HDAC classes. In particular, HDAC6 regulates acetylation of α-tubulin and the aggresome degradation pathway, and myeloma cells are susceptible to HDAC6 inhibition [20, 21]. Furthermore, inhibition of HDAC6 has minimal effect on histone biology and epigenetic events. Phase I trials of ricolinostat (ACY-1215), an HDAC6-specific inhibitor, in combination with bortezomib [22] or lenalidomide [23] showed promising efficacy, including in patients refractory to lenalidomide. Importantly, selective HDAC6 inhibition had an improved toxicity profile, with markedly less diarrhea and no QT prolongation compared with pan-HDAC inhibition with panobinostat. ACY-241 is another HDAC6 inhibitor with similar activity as ricolinostat in inhibiting HDAC6, but ACY-241 has the practical advantage of availability as a tablet instead of as a liquid, as with ACY-1215. There is an ongoing study of ACY-241 in combination with pomalidomide and dexamethasone, which has completed accrual (NCT02400242).

The FDA and European Medicines Agency approval of panobinostat offers an additional therapeutic option and is an important advance for the MM community. However, although panobinostat is associated with significant adverse events, there are trials ongoing to optimize the dosing of panobinostat and to identify its best partners in order to fully realize the potential of this drug class.

Disclosures

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Editor's Note:

See the related article, "EMA Review of Panobinostat (Farydak) for the Treatment of Adult Patients with Relapsed and/or Refractory Multiple Myeloma," by Kyriaki Tzogani et al. on page 631 of this issue.