Pharmacological Research 117 (2017) 185–191

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review

Deacetylase inhibitors as a novel modality in the treatment of multiple myeloma

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ARTICLE INFO

Article history:
Received 18 November 2016
Accepted 20 November 2016
Available online 21 November 2016

Keywords:
Multiple myeloma
Histone deacetylase inhibitors
Epigenetic modification

ABSTRACT

Deacetylase enzymes remove acetyl groups from histone and nonhistone proteins. Dysregulation of deacetylase activity is a hallmark of malignancy, including multiple myeloma (MM). Deacetylase inhibitors (DACi) cause epigenetic modification and inhibition of the aggresome pathway, resulting in death of MM cells. Panobinostat, a pan-DACi, has shown significant clinical benefit and is the first DACi approved for the treatment of MM. It is approved for use in combination with bortezomib and dexamethasone for the treatment of patients with relapsed or relapsed and refractory MM who have received ≥2 prior regimens including bortezomib and an immunomodulatory drug. Ricolinostat and ACY-241, which selectively inhibit HDAC6 and the aggresome pathway, are currently being studied in combination with dexamethasone and bortezomib or an immunomodulatory drug for the treatment of relapsed and refractory MM. In this review, we discuss the data from key clinical trials investigating deacetylase inhibitors as novel treatment options for MM.

Contents

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http://dx.doi.org/10.1016/j.phrs.2016.11.020
1043-6618/

1. Introduction

Histone deacetylases (HDACs) are a family of enzymes that regulate target protein activity through removal of acetyl groups [1]. Up to 1750 HDAC target proteins have been identified, including both histones and nonhistone proteins [2]. Dysregulated HDAC activity is an epigenetic hallmark of malignancy, including multiple myeloma (MM), resulting in aberrant gene expression and cellular signaling that promotes cell cycle progression, cell growth and survival, and resistance to apoptosis [3–5].

A total of 18 HDACs have been identified and grouped into 4 classes based on their homology to yeast HDACs, subcellular localization, and enzymatic activities [1,6,7]. Class I HDACs include HDAC1-HDAC3 and HDAC8, which are localized to the nucleus and primarily act on histone proteins and transcription factors. Class II HDACs include HDAC4-HDAC7, HDAC9, and HDAC10. They are thought to move between the nucleus and cytoplasm, where they act primarily on nonhistone proteins. Class III HDACs are sirtuins, which have differences in their catalytic mechanism and sequences compared with other HDACs. HDAC11, which is the only known class IV HDAC, displays features of both class I and II HDACs.

HDACs are commonly overexpressed in MM, and higher levels of class I HDACs, especially HDAC1, are associated with poorer prognosis [8]. Class I HDACs deacetylate histone lysine residues, resulting in a closed chromatin conformation that represses transcription [2,3]. HDACs also deacetylate nonhistone proteins, such as tumor suppressor p53, HSP90, STAT3, and NF-κB.

HDAC6 plays an essential role in protein degradation via the aggresome pathway [9]. HDAC6 binds to polyubiquitinated misfolded proteins and recruits them for transport to aggresomes, which are transported by microtubules to an autophagosome, where they are degraded via autophagy. This pathway is vital to MM cells that overproduce misfolded proteins and overburden the proteasome degradation pathway.

2. Mechanism of action of deacetylase inhibitors (DACi's)

Natural and synthetic DACi's exist. Some nonselectively inhibit a broad range of DACs (pan-DACi's), while others selectively target the clinically relevant DACs 1, 2, 3, and/or 6. Pan-DACi that have been studied in MM include panobinostat, vorinostat, and romidepsin; among these, panobinostat is the most potent and is the only one to have shown clinical benefit in MM [10–13]. Due to their lack of specificity, however, pan-DACi may lead to toxicities that limit time on treatment, particularly when used in combination with other agents with overlapping toxicities. HDAC6 inhibitors are also of interest in MM due to their inhibition of the aggresome pathway [14]. HDAC6 inhibitors being studied in MM include ricolinostat and ACY-241. Potency profiles of the DACi's being studied in MM are shown in Table 1.

DACi's bind to the catalytic domains of HDACs, downregulating their activity, which in turn inhibits myeloma cell survival and proliferation [16]. Class I DACi's acetylate histone lysine residues, opening chromatin for protein synthesis and gene expression. Agents that inhibit HDAC6 increase acetylation of tubulin and disrupt transportation of aggresomes, which leads to accumulation of protein aggregates and cell death [17].

Proteasome inhibition with bortezomib or carfilzomib can be used to effectively treat MM; however, MM cells can overcome proteasome inhibition by using the alternative aggresome pathway. Blockade of both the proteasome and aggresome pathways via combination therapy with proteasome inhibitors and DACi's has synergistic antitumor activity in MM [17]. Triple therapy with DACi, dexamethasone, and a proteasome inhibitor or immunomodulatory drug (IMiD) also results in synergistic deregulation of genes compared with each of the agents used as monotherapy [18].

3. Pharmacokinetics/Pharmacodynamics of panobinostat and ricolinostat

3.1. Panobinostat

Following administration of a single 20-mg dose of oral panobinostat, the drug is rapidly absorbed, with a time to maximum absorption of 2 h [19]. The median maximum concentration was 21.2 ng/mL, and the median area under the curve was 96 ng·h/mL. Panobinostat has a terminal elimination half-life of ≈ 30 h. The liver and kidney contributed similarly to the elimination of panobinostat, with mean percentages of unchanged panobinostat recovered in urine and feces of only ≈ 2% and 3%, respectively. Both cytochrome P450 and noncytochrome P450 enzymes may play a significant role in panobinostat metabolism, with minor contributions from CYP2D6 and CYP2C19. Panobinostat is extensively metabolized via reduction, hydrolysis, oxidation, and glucuronidation processes into at least 77 metabolites. Coadministration of bortezomib (1.3 mg/m^2) and panobinostat (20 mg) did not significantly affect the mean exposure of either agent, while coadministration of dexamethasone (20 mg) reduced panobinostat exposure by ≈ 20% [20].

3.2. Ricolinostat

Ricolinostat is rapidly absorbed and has a half-life of ≈ 3 h [21]. Exposure of ricolinostat increased dose dependently from 40 to 160 mg and then plateaued at doses ≥ 160 mg. Coadministration of ricolinostat (40–240 mg once daily [QD] or 160 mg twice daily [BID]) with bortezomib (1.3 mg/m^2) or lenalidomide (25 mg) did not significantly affect the pharmacokinetics of the individual agents [22–24]. In combination with bortezomib, ricolinostat's exposure increased with doses up to 240 mg QD [22]. When pomalidomide (4 mg) and ricolinostat (160 mg QD or BID) were coadministered, C_{max} of ricolinostat was reached ≈ 1 h after the first daily dose and then decreased to background levels within 6 h [25]. Pharmacodynamic analyses have demonstrated that following ricolinostat administration, the mean fold increase in acetylated tubulin is greater than for acetylated histone, indicating selective HDAC6 inhibition [21,23,25,26].

4. Clinical development of DACi's

4.1. Vorinostat + Bortezomib

The first completed phase 3 clinical trial of an HDACi in patients with MM was a randomized, double-blind, placebo-