Histone Deacetylase Inhibitors in Malignant Pleural Mesothelioma

Preclinical Rationale and Clinical Trials

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Abstract: Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer of the mesothelium with only a limited range of treatment options that are largely ineffective in improving survival. Recent efforts have turned toward the analysis of specific, dysregulated biologic pathways for insight into new treatment targets. Epigenetic regulation of tumor suppressor genes through chromatin condensation and decondensation has emerged as an important mechanism that leads to tumorogenesis. A family of histone acetyltransferases and deacetylases regulates this balance, with the latter facilitating chromatin condensation, thus preventing gene transcription, resulting in the loss of heterozygosity of tumor suppressors. Inhibition of this process, coupled with a similar inhibition of nonhistone protein deacetylation, ultimately leads to the promotion of apoptosis, cell cycle arrest, and inhibition of angiogenesis. An increasing amount of preclinical data highlighting the effectiveness of histone deacetylase inhibition in MPM cell lines and mouse xenograft models has led to a number of early phase clinical trials in patients with MPM. The results of these efforts have led to a multicenter, randomized, placebo-controlled phase III study of the histone deacetylase inhibitor vorinostat in patients with advanced MPM, offering hope for a new and effective therapy in patients with this disease.

Key Words: Pleural mesothelioma, Histone deacetylase inhibitor, Vorinostat.

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Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer that arises from the mesothelial cells that line the pleural cavity. The incidence in the United States has increased over time, with 2000 to 3000 cases now diagnosed annually. The mortality rate is high: more than 80% of patients present with late stage disease, and the median survival does not exceed 12 months.[1] Its association with asbestos exposure was first recognized in 1960.[2] Studies using Surveillance, Epidemiology, and End Results data show current and predicted incidences of disease mirroring trends in asbestos use during the last century, with a latency of 20 to 40 years between peak consumption in the 1950s and 1960s to peak incidence of disease during this decade.[3,4]

The current treatment options for patients with MPM are limited and largely ineffective. Surgical options include thoracoscopy for palliation, pleurectomy/decortication, and extrapleural pneumonectomy, the last two of which can be offered in only a minority of patients, both for reasons of advanced disease and comorbid conditions.[5–8] More recently, the use of induction chemotherapy before extrapleural pneumonectomy and postoperative radiation therapy has shown promise for improved outcomes.[9,10] With regards to systemic therapy, a great number of early phase trials of chemotherapy and novel therapeutics have been conducted, but with disappointing results.[11] Phase III trials have demonstrated improved survival with an antifolate plus cisplatin over treatment with cisplatin alone.[12,13] Although these data provided the basis for a new standard in the first-line treatment of patients with unresectable disease, survival was improved by only a few months, and overall survival remains poor. The search for new, effective therapies that capitalize on the biology of MPM continues.

Epigenetic Regulation

Epigenetic modification has emerged as an important mechanism leading to tumorogenesis. These changes, distinct from the processes of mutagenesis, maintain a degree of heritability that provide the cancer cell an additional means by which to avoid the regulatory mechanisms that limit cell growth and proliferation. Both hypermethylation and histone regulation have been linked to the development of MPM. Data supporting the former, in which CpG islands within gene promoters are methylated and silenced, is sparse and based on the identification of simian virus 40 viral sequences in mesothelioma cell lines and tumor samples, with increased tumor suppressor gene methylation found in simian virus 40 large T-antigen containing

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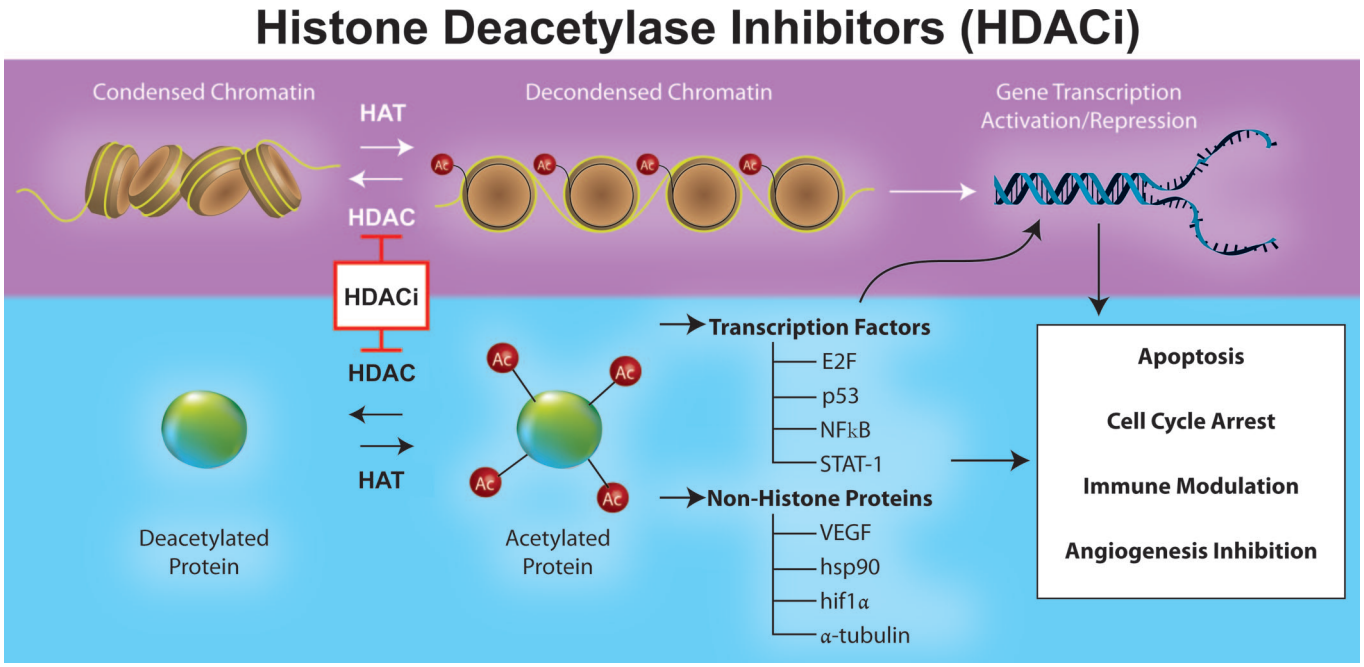

FIGURE 1. Schematic representation of the targets and effects of HDAC inhibitors (HDACi). In addition to directly regulating transcription through changes in chromatin structure, HDACi modulate the acetylation of transcription factors and other non-histone proteins, leading to a range of biologic effects, including the promotion of apoptosis, cell cycle inhibition, immune modulation, and inhibition of angiogenesis.

specimens.[14,15] Data for the latter is more robust and helps to provide a basis for ongoing trials in MPM using inhibitors of histone deacetylation.

Histones are a family of basic proteins that serve as structural and regulatory components of chromatin. Chromatin is comprised of DNA, RNA, and both histone and non-histone elements and serves to pack linear DNA efficiently within the cell. The fundamental subunit of chromatin is the nucleosome, which winds 147 bp of DNA around an octamer of histone subunits.[16] Transcriptional activity can only occur when nucleosomes are decondensed as euchromatin, in a process that couples methylation of DNA with, among other reactions, methylation, acetylation, and phosphorylation of histones (Figure 1, top).[16]

Among these biochemical modifications, histone acetylation, controlled by a family of acetyltransferases and deacetylases (HDACs), has emerged as clinically important.[17] Much of this interest has focused on HDACs, which serve to remove lysine residues from histone tails and non-histone proteins, thereby preventing chromatin relaxation and gene transcription (Figure 1, left). Four classes of HDACs have been characterized, grouped in part by homology and in part by cellular localization, with aberrant recruitment and overexpression found in a wide range of cancers.[18–25] A host of pharmacologic inhibitors have also been identified, divided by both structure and specificity for the different classes of HDACs.[26]

Histone Acetylation and MPM

In vitro data for the role of HDAC inhibition in MPM has centered on apoptosis, although the biologic effects of HDAC inhibitors (HDACi) are diverse and include cell cycle arrest, angiogenic inhibition, immunomodulation, and direct acetylation of signaling intermediates and transcription factors (Figure 1, bottom).[26] The relevant studies include work by Cao et al.,[27] who found a decrease in the expression of the antiapoptotic protein bcl-XL and the induction of apoptosis in MPM cell lines treated with sodium butyrate. Suberoylanilide hydroxamic acid was also found to sensitize MPM cells to TNF-related apoptosis-inducing ligand-mediated apoptosis, with strong down-regulation of bcl-XL.[28] Depsipeptide was similarly cytotoxic to MPM cells, an effect synergistically increased with flavopiridol, a cyclin dependent kinase inhibitor.[29]

More recently, caspase-dependent apoptosis has emerged as an important mechanism. Treatment of TNF-related apoptosis-inducing ligand-induced MPM cell lines with the HDACi LBH589 was found to increase caspase 3 and 7 expression in addition to apoptosis. This expression was linked to the degradation of the antiapoptotic protein X-linked inhibitor of apoptosis protein.[30] Similarly, treatment of MPM cell lines with valproic acid increased caspase-dependent apoptosis when coupled with cisplatin and pemetrexed.[31] This work by Vandermeers et al. was important in its study of HDACi alone and in combination with chemotherapy. In particular, while chemotherapy reliably led to increased annexin V staining and an increase in the sub-G1 population, HDACi monotherapy did so in only one of three cell lines tested. In addition, treatment with valproic acid plus chemotherapy led to a synergistic increase in reactive oxygen species formation and annexin