



Vorinostat: A Novel Anti Cancer Drug

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Introduction

Medical management of most of the cancers is far from satisfactory. Therefore the need for newer drugs with varied mechanism of action is the need of the hour to overcome this obstacle. The basic approach to cancer treatment is shifting from direct cytotoxic activity to other avenues. Newer approaches like genetic therapies and biological response modifiers are being tried to tackle the cancerous cells. Apoptosis or programmed cell death is an essential physiological process for the regulation of development and maintenance of homeostasis in adult tissue. Low rate of apoptosis may promote survival and accumulation of abnormal cells that can give rise tumor formation. Similarly one of the major characteristic of cancer cells is loss of differentiation. Therapies targeting apoptosis and cell differentiation are now being tried clinically. New class of agents known as histone deacetylase inhibitors induce growth arrest, cell differentiation, and apoptosis of tumor cells (1).

Vorinostat (suberoylanilide hydroxamic acid) is the first drug in this new class approved for the treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL). It causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells (1,2).

Chemistry

Vorinostat is described chemically as *N*-hydroxy-*N'*-phenyloctanediamide. The empirical formula is $C_{14}H_{20}N_2O_3$ (1).

Mechanism of Action (1,2)

Vorinostat is a potent histone deacetylase inhibitor that blocks the catalytic site of these enzymes. A large number of cellular proteins are modified post-translationally by acetylation, leading to altered structure and/or function. Many of these proteins, such as core nucleosomal histones and transcription factors, function in key cellular processes and signal transduction pathways that regulate cell growth, migration, and differentiation. At concentrations that are non-toxic to normal cells, vorinostat dramatically alters

cellular acetylation patterns and causes growth arrest and death and in a wide range of transformed cells, both in vitro and in animal tumor models (2).

Regulation of gene expression is mediated by several mechanisms such as DNA methylation, ATP-dependent chromatin remodeling, and post-translational modifications of histones. Epigenetic changes in gene expression may play an important role in cancer growth. The opposing activities of histone acyltransferases (HATs) and histone deacetylases (HDACs) regulate gene expression by altering chromatin structure. HATs, by acylating histones, produce an open chromatin structure, resulting in greater accessibility of regulatory proteins to DNA. HDACs, by contrast, catalyze acyl group removal, leading to a closed chromosomal configuration and transcriptional repression (2). HDAC inhibition may permit re-expression of proteins that promote apoptosis and cell differentiation while inhibiting cell cycling and cell division (1). Vorinostat inhibits HDAC by binding to a zinc ion in the catalytic domain of the enzyme. Vorinostat demonstrated activity in murine xenograft models and it was additive or synergistic when combined with chemotherapy drugs in induction of differentiation and apoptosis of various cancer cell lines.

Pharmacokinetics (1)

Vorinostat is administered orally with food as high-fat meal increases (33%) the extent of absorption. It is approximately 71% bound to human plasma proteins. The major pathways of vorinostat metabolism involve glucuronidation and hydrolysis followed by α -oxidation. Two pharmacologically inactive metabolites *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid are produced. Vorinostat is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes. Renal excretion does not play a role in the elimination of vorinostat.

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Safety profile

The most common adverse reactions due to vorinostat include gastrointestinal symptoms like diarrhea, nausea, anorexia, weight decrease, vomiting, constipation and constitutional Symptoms like fatigue and chills. Thrombocytopenia, anemia, dysgeusia and dry mouth is also seen in patients

Indication

Vorinostat is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

Drug interactions

1-Coumarin-Derivative Anticoagulants. Vorinostat was seen to prolong prothrombin time (PT) and International Normalized Ratio (INR) in patients receiving concomitant coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered vorinostat and coumarin derivatives.

Clinical Trials

Vorinostat (suberoylanilide hydroxamic acid) is the first FDA-approved HDAC inhibitor for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). In two Phase II trials, vorinostat 400 mg/day was safe and effective with an overall response rate of 24-30% in refractory advanced patients with CTCL including large cell transformation and Sézary syndrome. In all treated patients, the objective response was 24.2% (8/33) in the overall population, 25% (7/28) in patients with Stage IIB or higher disease and 36.4% (4/11) in patients with Sezary syndrome (3).

Vorinostat, a histone deacetylase inhibitor, represents a rational therapeutic target in glioblastoma multiforme (GBM). In one of the recent trial it has shown very promising results (4).

Vorinostat has shown preclinical activity in non-small cell lung cancer (NSCLC). No objective antitumor activity was detected with single agent vorinostat in a clinical trial; however, it yields time to progress in relapsed NSCLC similar to that of other targeted agents (5).

Heat shock protein (hsp) 90 inhibitors promote proteasomal degradation of pro-growth and pro-survival hsp90 client proteins, including CDK4, c-RAF and AKT, and induce apoptosis of human lymphoma cells. The pan-

histone deacetylase inhibitor vorinostat has also been shown to induce growth arrest and apoptosis of lymphoma cells. Combined treatment with DMAG and vorinostat synergistically induced apoptosis of the cultured MCL cells, as well as induced more apoptosis of primary MCL cells than either agent alone (6).

Future Prospects

Vorinostat has shown promising clinical activity against the treatment of advanced solid tumors, colorectal cancer, hematological malignancies and recurrent glioblastoma multiforme (7-10) at doses that have been well tolerated by patients.

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