

Histone Deacetylase Inhibitors in Cancer

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ABSTRACT

The epigenetic modifications can change the state of a part of the DNA by different enzymes such as the histone deacetylases. Dysregulation of the epigenetic mechanisms is associated with the initiation and progression of cancer. The reversibility of this dysregulation in epigenetic modifications makes it an attractive target for cancer therapy and drug discovery scientists. We conducted a computerized Literature search involving human subjects, published in English until December 2017, and indexed through Medical Databases; MEDLINE/PubMed, EMBASE, and Web of Science. We reviewed articles performed for prospective and other types of studies related to histone deacetylases inhibitors which can help cancer patient's status during the therapy. Several investigational drugs for cancer therapy are in clinical trials. Interestingly, US Food and Drug Administration has already approved four histone deacetylases inhibitors drugs for hematological malignancies but not for solid tumors. Currently, different histone deacetylases inhibitors are under study for both hematological and solid tumors as single agents or in combinations. In this review, we will discuss some the approved histone deacetylases inhibitors, and the one in clinical trials.

Keywords: Histone, Deacetylase, Cancer, Epigenetic

INTRODUCTION

The structure of chromatin is responsible for the accessibility of DNA to transcription factors. Therefore it is essential to determine the activity of genes. The N- and C-terminal tails of histones undergo reversible post-translational modifications, which will cause a change in the interaction between the histones and the DNA. These modifications include methylation, acetylation, phosphorylation, glycosylation, and are related to the difference in the structure of chromatin. The histone tails are accessible to a different type of enzymes with various functions. For example, histone acetyltransferases (HATs), histone deacetylases (HDACs), and kinases can add or remove covalent modifications and are called writers and erasers. Proteins that can understand the histone code are known as readers.

Epigenetic changes make a set of labels, which give information about the local state of the chromatin and define as the histone code. This covalent modification of the histone tails leads to activation and silencing of transcription state of the chromatin depending on the type and place of the changes. HATs mediate the acetylation of histones H3 and H4. This acetylation results in removing the positive charge of a lysine residue in histone, causing chromatin accessibility and eventually helping the access of transcription factors to genes^[1].

Histone deacetylases (HDACs) are enzymes, which remove the acetyl groups from histone and other proteins. HDACs enzymes can be classified into four categories. The classical HDACs are those enzymes which have been concerned in

tumorigenesis and are targets of the epigenetic drugs in the clinics. Class I HDACs include HDAC1, HDAC2. They are restricted to the nucleus of the cells, and they have different substrates including proteins like p53 and E2F. Class II HDACs can be classified into class IIA and IIB. They differ in their substrates and their localization in the cell^[2].

Histone Modification in Cancer

Global loss of acetylated histones occurs during cancer development and progression. This loss of histone acetylation by HDACs enzymes will result in gene repression. HDAC enzymes are usually found overexpressed in several types of cancer, which make them highly affected by epigenetic therapy. HAT enzymes and HDACs enzymes which work together in histone acetylation levels maintaining are altered in cancer as well. Abnormal fused proteins are formed by the translocation of chromosome of histone acetyltransferase and its genes occur in leukemia, e.g. MOZ, and p300. This fusion protein can lead to global alterations in histone acetylation level and patterns in cancer^[3].

METHODOLOGY

We conducted a computerized Literature search, published in English until September 2017, and indexed through Medical Databases; MEDLINE/PubMed, EMBASE, and Web of Science. We reviewed articles performed for prospective and other types of studies related to histone deacetylases inhibitors. Searching relevant

articles and discussing the results to allow meaningful rate comparison, and to conclude a result view which benefits the cancer patients. The search strategy combined the following terms and keywords: “histone,” “cancer,” “epigenetic,” “deacetylases.” When more than one publication was identified referring to the same result data, the first publication was selected. Non-English articles excluded which did not fulfill inclusion criteria, and they were therefore not considered eligible for inclusion in the study. Furthermore, we searched the reference lists of articles identified by this search. **The study was approved by the Ethics Board of UNIVERSITY OF DEBRECEN.**

Approved Histone deacetylase inhibitors (HDACIs):

The antitumor mechanism of action of histone deacetylase inhibitors is the increased acetylation of histones. However, clinical trials have shown that there is an increase in acetylation with little clinical effect in tumor samples. Therefore, these drugs have a different mechanism of action which will lead to different effects such as the arrest of cell cycle, the initiation of the apoptotic pathway, the activation of autophagy, reactive oxygen species generation, and angiogenesis^[4].

Vorinostat

Food and Drug Administration considered Vorinostat as approved drug for cutaneous T-cell lymphoma (CTCL) in patients with recurrent chronic conditions. A phase II study with 74 candidates (in stage IB and higher CTCL) which was a single-arm trial helped approving this drug. The recommended dose was 400 mg, which can be changed to 300 mg for overdose reasons. The primary endpoint was an objective response which was 30%. Furthermore, common clinical adverse events (AEs) were fatigue and pulmonary embolism. Additionally, some hematologic laboratory abnormalities, e.g., thrombocytopenia^[5,6].

Romidepsin

The U.S. FDA approved romidepsin in 2009 for the treatment of cutaneous T-cell lymphoma in those patients who treated with previous one systemic treatment. In 2011, The U.S. FDA approval of romidepsin for the treatment of relapsed/refractory PTCL was primarily based on a trial enrolled 131 patients with PTCL after a previous systemic treatment. Complete response (CR)/unconfirmed CR (CRu) was the primary endpoint, and 25% (33 of 130), including 19

patients (15%) with CR/Cru was the objective response rate. 14 mg/m² was the recommended dose during a four hours infusion. Common side effects were neutropenia, infections, anemia, and fatigue^[7,8,9].

Belinostat

In 2014, belinostat was approved by the U.S. FDA for refractory/relapsed PTCL treatment. A phase II trial in patients with relapsed/refractory PTCL with the primary endpoint of overall response rate (ORR) was helping the approval of this drug. There were 129 patients included, and the ORR was 26% with a dose of 1000 mg/m²/day. In this study, no infusion reactions were reported. The most commonly reported serious side effects were pneumonia, infection, anemia and, thrombocytopenia^[10,11].

Panobinostat

In 2015, panobinostat in addition with bortezomib and dexamethasone was approved by U.S. FDA for multiple myeloma treatment in patients with two previous treatments. The approval was based on a Phase III trial; there were 768 patients included in a placebo-controlled study. The median progression-free survival (PFS) was increased. The dose of panobinostat is 20 mg orally. Panobinostat is well tolerated but, neutropenia, diarrhea, thrombocytopenia was observed as side effects. And diarrhea was the most significant adverse event in the study^[12,13].

Histone deacetylase inhibitors (HDACIs) in Clinical Trials:

Clinical Trials on Solid Tumors

Vorinostat

Vorinostat was used in patients with head and neck cancer, and it works by HDAC inhibition. In phase II study thirteen patients were enrolled with no responses were observed, only single unconfirmed partial response was seen. Therefore, vorinostat did not demonstrate significant efficacy^[14]. In addition a different phase II study for patients with metastatic breast cancer showed no partial or complete responses but only stable disease, which did not indicate adequate single-agent activity of vorinostat in this group of patients^[15]. Vorinostat was also tested for the treatment in patients with epithelial ovarian carcinoma in a phase II clinical study: two of the 27 patients enrolled have survived, with one having a partial response. The result shows minimal activity for vorinostat as single agent in this group of patients^[16]. Based on preclinical studies, vorinostat

can reverse tamoxifen resistance in breast cancer. In a phase II trial vorinostat was recommended to be used with tamoxifen for the treatment of patients with breast cancer. Forty-three patients were enrolled and the objective response was 19% and the clinical benefit rate was 40%, and median response duration was 10.3 months. Vorinostat together with tamoxifen showed high activity in reversing hormone resistance and a future treatment for this group of patients^[17]. For the treatment of patients with advanced non-small-cell lung cancer (NSCLC) during another phase II study, vorinostat was studied in a combination of carboplatin and paclitaxel versus placebo for patients with advanced non-small-cell lung cancer. Ninety-four patients initiated protocol therapy, vorinostat showed 34% of confirmed response rate versus 12.5% with placebo. Six months was the median progression-free survival for the vorinostat group versus 4.1 months for the placebo group and overall survival for the vorinostat group was 13.0 months versus 9.7 months for the placebo. Vorinostat working great with carboplatin and paclitaxel in patients with advanced NSCLC and improving the efficacy of them so it is a promising drug for the treatment of NSCLC^[18].

Belinostat

In a phase II clinical trial, women with ovarian cancer like platinum-resistant epithelial ovarian cancer and micropapillary ovarian tumors were treated with the HDAC belinostat. This trial enrolled 18 patients with epithelial ovarian cancer and 14 patients with micropapillary (LMP) ovarian tumors. One patient with micropapillary low malignant potential (LMP) tumor had an unconfirmed partial response (uPR), and 10 had stable disease (SD). About 13.4 months was the progression-free survival (PFS). In the epithelial ovarian cancer group, nine patients had stable disease (SD), and median PFS was 2.3 months^[19]. In another phase II clinical trial, belinostat was used to treat advanced thymic epithelial tumor cases. Forty-one patients were enrolled, 25 had thymoma, and 16 had thymic carcinoma. Two of the thymoma group patients achieved partial response (response rate, 8%), 25 had stable disease and no responses in patients with thymic carcinoma. This result demonstrates minimal activity of belinostat in this group of patients^[20].

A phase II trial studied the combination of belinostat and carboplatin in the treatment of recurrent or persistent platinum-resistant ovarian cancer; and the ORR was the primary endpoint.

Twenty-nine patients were enrolled in the study, but only 27 were evaluable.

The result showed one patient with complete response, and another with a partial response, for an ORR of 7.4%. Patients had stable disease were twelve and had increasing disease were eight. The median PFS was 3.3 months, and overall survival was 13.7 months. This study suggests that the combination of belinostat and carboplatin had a low activity in this group of patients^[21].

Entinostat

Entinostat is tested by a clinical study which enrolled 130 patients for the treatment by exemestane with entinostat or with placebo in women with estrogen receptor-positive breast cancer. The median progression-free survival (PFS) and the overall survival both were improved in the entinostat group. Fatigue and neutropenia were the most frequent side effects. The result indicates that entinostat was well tolerated and demonstrated little activity in breast cancer patient^[22]. In another combination, in a phase II clinical trial of entinostat and erlotinib was given to patients with lung cancer. The result indicated that this combination is not effective for lung cancer patients^[23].

Romidepsin

In a phase II trial of romidepsin, 14 patients with head and neck cancer were included. Unfortunately, no responses observed but some patients record stable disease. This trial results showed the limited activity of romidepsin alone for the treatment of head and neck cancer^[24]. In another clinical study of romidepsin, 35 patients who have metastatic prostate cancer were enrolled. The administered dose was iv 13 mg/m² over four hours on days 1, 8 and 15 every 28 days. Two patients reached a confirmed radiological partial response based on (RECIST) that lasted for at least six months and prostate-specific antigen decline of more or equal 50%. The trial showed minimal antitumor activity at this dose^[25]. another phase II study showed the same previous result for the treatment of small cell lung cancer^[26].

Valproic acid

In 2011, a randomized phase III trials was published; for the use of hydralazine combined with valproate in cervical cancer. There were 36 patients enrolled, with an average of six cycle. Four partial responses was seen ; the median PFS ten months. Combination of hydralazine and valproate show a promising anti tumors activity in this trial^[27]. Valproic acid was also studied for the treatment of

low-grade neuroendocrine carcinoma. In this phase II clinical trial, eight patients were enrolled. Only one record unconfirmed partial response (uPR)^[28]. Previous studies suggested that valproic acid and doxorubicin to have a proapoptotic effect and can induce apoptosis mesothelioma. The result of a phase II clinical trial show seven partial responses and the best disease control rate was 36%. The result demonstrates an effective chemotherapy against this group of patients^[29]. In phase II study for the treatment of glioblastoma, the combination of valproic acid with radiation therapy and temozolomide show favorable activity^[30].

Panobinostat:

Panobinostat was administered intravenously for 21 patients with lung cancer in a phase II study. The primary endpoint was the response rate. Two cases showed reductions more than 30% at first assessment (week 6), and there were three with stable disease at 10, 12, and 13 weeks of the 19 evaluable patients for efficacy. Although the study was stopped early because of a lack of activity, weak clinical activity of panobinostat combined with a safe profile permits further exploration of the potential in this group of patients^[31]. It also showed a disappointing result for the treatment of prostate cancer as monotherapy^[32]. In a phase II study in combination with bevacizumab for treatment of recurrent glioblastoma, the combination shows limited benefit^[33].

Pracinostat:

The result was also disappointed in a phase II clinical trials, 32 patients were treated by pracinostat for the castration-resistant prostate cancer^[34]. Moreover, in another phase II study for the treatment of sarcoma was stopped because of limited availability of the drug and no objective response^[35].

Clinical trials in hematological tumors

Givinostat:

Givinostat was studied for the treatment of patients with chronic myeloproliferative neoplasm. In phase II study, 32 patients were enrolled who record complete and partial responses for different types of neoplasm. Givinostat was well tolerated, and the result demonstrates that it can induce antitumor activity in most polycythemia vera and some myelofibrosis patients. This result indicates antitumor activity of this agent against myelofibrosis patients^[36]. In another phase II trial, 44 patients with polycythemia vera were enrolled who were unresponsive to the maximum tolerated

doses of hydroxycarbamide. Therefore, they received 50 or 100 mg/day dose of Givinostat in combination with the maximum tolerated doses of hydroxycarbamide. Haematological response rate at week 12 was the primary endpoint. Responses were observed in 23 patients, but two patients only record complete response. The result showed that the combination of Givinostat and hydroxycarbamide was clinically effective in this group of patients with polycythemia vera^[37].

Panobinostat:

In a phase II study, 129 patients with Hodgkin lymphoma were enrolled. Panobinostat was given orally three times per week at a dose of 40 mg and reduction of the tumor occurred in 96 patients (74%), and the objective response was 27% (35 patient), 30 patients have partial responses, and 4% have complete responses. side effects like thrombocytopenia, anemia, and neutropenia were controllable. The trial's result showed that panobinostat as single agent indicates antitumor activity and durable responses^[38].

Mocetinostat

In this phase II study, mocetinostat was administered for patients Hodgkin lymphoma. This treatment result in two complete and 12 partial responses. There were Twelve patients stopped treatment because of adverse effects. Common side events were fatigue and pneumonia. This study has been terminated because of the death of four patients during the study. The result showed that mocetinostat has promising clinical activity as monotherapy with manageable toxicity^[39]. Mocetinostat was given to a patient with chronic lymphocytic leukemia as a monotherapy in phase II clinical trial, but the result show limited activity^[40].

Romidepsin:

Romidepsin was given to patient for the treatment of refractory multiple myeloma. In this phase II trial, 13 patients were enrolled, and no one reach objective response^[41].

DISCUSSION

Promising preclinical and clinical trials, as well as the proven clinical effect of histone deacetylase inhibitors by US FDA, give us an optimistic view of the future of histone deacetylase inhibitors development by drug discovery scientists. Table 1 summarizes the approved histone deacetylase inhibitors by the US FDA .More preclinical studies and clinical trials will be needed to increase the efficacy of these agents, and to set the dose and the dosing schedule. Furthermore, we need to identify

the signaling pathways in every type of tumors in personalized patient profiles for the best use of these drugs in the treatment of cancer and especially for solid tumors where the clinical result is disappointing.

It is very common to find regions of hypoxia in solid tumors. These areas of hypoxia make solid tumors more aggressive and resistant to therapy. Cells in those hypoxic areas of solid tumors have a distinct epigenetic profile. Therefore, because this different epigenetic pattern it is essential to study the epigenetic drugs on those type of tumors to test them under hypoxic conditions. These tests, if done before clinical trials, will provide a high expectation of the drug's effect in solid tumors^[42].

Another explanation of the disappointing results in solid tumors is that outcome is assessed based on

the response evaluation criteria in solid tumors (RECIST). The RECIST evaluation system is not a good indicator of activity for epigenetic drugs. Epigenetics involves different mechanisms in the cell, which will take time before we can reach its final benefits^[43].

Two important future methods in the trials of epigenetic drugs have been suggested. Firstly, testing of epigenetic medications under hypoxic conditions before clinical trials in solid tumors. Secondly, generate new criteria for the evaluation of epigenetic drugs in solid tumors to get more reliable information about the long-term results of those trials. The combinations of those two ideas may result in positive results of clinical trials for solid tumors.

Drug	Approved by U.S. FDA for	Year	Common adverse events	References
Vorinostat	cutaneous T-cell lymphoma (CTCL)	2006	Fatigue,pulmonary embolism,thrombocytopenia	5
Romidepsin	cutaneous T-cell lymphoma (CTCL) peripheral T-cell lymphoma (PTCL)	2009 2011	neutropenia,infections, anemia, and fatigue	7
Belinostat	peripheral T-cell lymphoma (PTCL)	2014	pneumonia,infection, anemia, thrombocytopenia	10
Panobinostat	multiple myeloma In combination with bortezomib and dexamethasone for the treatment of	2015	Neutropenia,diarrhea, thrombocytopenia ,diarrhea	12
[Table/Fig-1]: Summary of the Approved Drugs. U.S. FDA: US Food and Drug Administration				

CONCLUSION

Developments made in the cancer epigenetics prove that this therapy is potentially important to regulate the abnormality in the epigenome. This review highlights the use of histone deacetylases inhibitors in cancer therapy. We focused on the approved drugs and the drugs in clinical trials. While four histone deacetylases inhibitors are already approved for hematological malignancies, there are many drugs in different phases of clinical trials for both haematological and solid tumors. Those drugs are in clinical trials either as single agents or in a combination therapy. Result of these studies clearly prove the potential in cancer therapy.

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