HISTONE DEACETYLASE INHIBITORS; AN OVERVIEW OF THE CLINICAL STUDIES IN HEMATOLOGICAL MALIGNANCIES AND SOLID TUMORS

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ABSTRACT

Histone deacetylase inhibitors (HDACi) are considered novel potential drugs in cancer treatment and so far, they represent an important area of research. Four HDACi, Romidepsin, Belinostat, Vorinostat and Panobinostat have been currently approved by the U.S FDA as anticancer agents,3 and many others are in ongoing clinical trials. Over the last decades, histone deacetylase enzymes (HDACs) have been recognized as therapeutic targets, due to the correlation between irregular covalent modifications catalyzed by them and tumor development. The rationale for developing HDACi is based on their ability to induce differentiation, apoptosis and cell cycle arrest in cancer cells. Objectives: This review aims to summarize the recent progress toward HDACi evaluating their efficacy as single agents, or in combination with other chemotherapeutic agents for the treatment of different types of tumors. A literature research was conducted in MedLine, PubMed, Caplus, SciFinder Scholar databases from 2015 to 2021. The overall future for the use of HDACi in combinatory regimens in a variety of malignancies, looks promising, although more information regarding life quality changes associated with the administration of these agents, should be forthcoming. So far, poor outcomes have been reported in the treatment of solid tumors by using HDACi as single agents, meanwhile, they have shown distinguished effectiveness in the treatment of hematological malignancies. The use of HDACi in combinatory anticancer regimens is considered a successful strategy in

terms of lower toxicity and better clinical outcomes. Although, a better comprehension of HDACi effectiveness is required in order to optimize their efficacy, toxicity and overcome therapy resistance.
Keywords: epigenetic factors, HDACs, HDACi, clinical trials, novel anti-cancer therapies, FDA, efficacy, combination therapy.

1. INTRODUCTION

Cancer is considered an essentially genetic disease, in which genomic expression alterations alter the cellular control pathways causing the cell to proliferate in an uncontrolled way (Baylin and Jones, 2016). However, in recent decades, numerous clues have led to the recognition that epigenetic factors may also be critical in the evolution of human cancer (Porta-Pardo *et al*., 2020).

Among the post-translational modifications of chromatin, which results in the creation of various gene expression patterns, histone acetylation is one of the most studied processes and appears to play a fundamental role in the regulation of nucleosomes (Tolsma and Hansen, 2019). In fact, the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs) were identified among the transcriptional coactivators and corepressors, respectively, providing strong evidence of the functional connection between histone acetylation and transcription (Sanei and Kavoosi, 2019; Milazzo *et al*., 2020).

A critical event contributing to tumor formation seems to be the imbalance between HATs and HDACs, resulting in an abnormal HDAC activity leading to transcriptional repression of specific genes that promote tumor suppression (Fraga and Esteller, 2005). Despite the HDACs catalytic activity in removing the acetyl groups from the ε-amino lysine residues on histones, they also deacetylate several non-histone proteins (Li and Seto, 2016; Porter and Christianson, 2019). Thus, the idea emerging from this scenario was that the use of HDAC inhibitors (HDACi) might be a useful approach to cancer therapy (Singh *et al*., 2018).

Currently, in humans, there have been identified 18 HDAC family members which are classified into four classes based on sequence homology to yeast HDACs (Mottamal *et al*.,2015; Lee *et al.*, 2021). Class I includes HDAC1, -2, -3, and -8, which are primarily situated in the nucleus of the cells (Gregoretti *et al*., 2004; Brosch *et al*., 2008; Li *et al.*, 2020). Class II HDACs are further subdivided into: class IIa (HDAC enzymes 4,5,7, 9) and class IIb (HDAC 6, 10). Class III Sir 2-like enzymes (human sirtuins 1–7), and class IV (HDAC11) (Trapp and Jung, 2006; Wang *et al.*, 2011; Tang *et al.*, 2013; Zhang *et al.*, 2017; Zhang *et al.*, 2019). Classes I, II and IV are zinc-dependent metalloproteins and they are present in the nucleus or cytosol,

while the class III HDAC family requires NAD+ as a co-factor and they appear in the cytoplasm, mitochondria or nucleus of the cell (Marks and Xu, 2009; Alexander *et al.*, 2019).

The HDAC inhibitors are generally classified into benzamides [compounds such as Entinostat, Mocetinostat, Ci-994, Tacedinaline, 4SC202], hydroxamates [such as Vorinostat, Panobinostat, Belinostat, Givinostat, Trichostatin, Resminostat, Quisinostat, Abexinostat, Practinostat, CHR-3996], depsipeptides [Romidepsin], short chain fatty acids [such as Valproate, Pivanex, Sodium phenyl butirate] and sirtuins inhibitors [Nicoitinamide, sirtinol, Cambinol, EX-527] (Miller *et al*., 2003; Ceccacci and Minucci, 2016; Eckschlager *et al*., 2017). The majority of HDACi, present a common recognition domain (called "cap"), linked to a hydrophobic chain which bears a zinc-binding group (ZBG) of different nature (Ni *et al.*, 2015). Based on their isoform specificity, they are classified into; selective HDAC inhibitors and pan-inhibitors, which act on all HDAC classes (Ceccacci and Minucci, 2016). Following the discovery of dose-limiting toxicity of pan HDAC inhibitors, there has been a trend toward the development of class-specific HDAC inhibitors to improve the outcomes and limit the toxic effect (Eckschlager *et al.*, 2017).

Yadav *et al.*, (2019) stated that clinical studies report that class III and IV HDAC inhibitors appear to have some adverse effects such as thrombocytopenia, neutropenia, anemia, fatigue, and diarrhea. Meanwhile, class II HDAC inhibitors are considered promising agents, but due to several side effects associated with their use, such as cardiac toxicity, therefore more data is needed in order to progress with their application in cancer therapy (Manal *et al*., 2016; Zhang *et al.*, 2017).

To date, selective Class I HDAC inhibitors are the most investigated isoforms, since they are highly expressed in several cancers as well due to their limited toxic effects.

The ongoing intense research conducted in this field has shown that HDACi have a complex anticancer activity exerted through multiple pathways from their interaction with histone deacetylases to numerous other molecular targets (Hull *et al.*, 2016; Karagiannis and El-Osta, 2006).

Several clinical trials performed during the last years proved that HDACi compounds are potent inducers of growth arrest, differentiation, cell death by autophagy/apoptosis, accumulation of ROS and inhibition of angiogenesis in transformed cells (Bolden, 2006; Mehnert and Kelly, 2007; Jazirehi, 2010; Cheng *et al.*, 2017). Furthermore, the selective toxicity of HDACi on mutated cells and their ability to synergistically promote the efficacy of many conventional chemotherapeutic agents has aroused further interest in this new category of drugs (Suraweera *et al.*, 2003; Diyabalanage, 2013).

To date, there are four HDACi agents approved by the USA Food and Drug Administration for the treatment of different type of tumors and many others are being evaluated in preclinical or clinical studies (Vander Molen *et al.*, 2011; Autin *et al.*, 2019). Vorinostat (SAHA) was approved by the USA FDA in 2006 for the treatment of CTCL followed by Romidepsin (FK228), approved for the treatment of Cutaneous T-cell Lymphoma, (CTCL) and Peripheral T-cell lymphoma (PTCL) three years later. Belinostat (PXD 101) and Panobinostat (LBH-589) have been recently approved (2014 and 2015 respectively) for the treatment of PTCL and Multiple Myeloma (MM) (Chun, 2015; Guha, 2015; Yoon and Eom, 2016; Li and Sun, 2019).

The present paper aims to provide a comprehensive and updated overview of the current state-of-the-art of different U.S. FDA-approved HDACi, as well as the recent progress toward combination with other chemotherapeutic agents in the treatment of a variety of tumors.

2. METHODS AND MATERIALS

This manuscript is a descriptive review based on previous research papers. In order to provide an overall picture of recent advances on the topic, a broad literature review of only published studies over the period 2015-2021, was performed. The selected databases were as follows: PubMed, MEDLINE, CAPLUS and SciFinder Scholar. In addition, the keywords and phrases used to generate this research were: epigenetic factors, HDACs, HDACi, FDA, clinical trials, novel anti-cancer therapies.

3. RESULTS

As it has been previously reported in the literature, despite the approval by the FDA, HDACi have been shown to have limited therapeutic efficacy against solid tumors as single therapeutic agents. Thus, combining HDACi with other conventional drugs is being considered an important approach toward their full therapeutic potential benefits (Vancurova *et al.*, 2018).

- ***Vorinostat (SAHA)*** belongs to the hydroxamate derivates class and causes inhibition of both class I and II HDACs (Park *et al.*, 2017). It has been approved for the treatment of CTCL with a daily recommended dose of 400 mg.

Numerous clinical trials have been performed and others are planning to evaluate the use of this compound in monotherapy or in combination for the treatment of hematological and solid tumors (Chun, 2016; Wang *et al*., 2020).

Other investigations were conducted considering the possible combination of HDACi with other agents based on promising results which indicate the ability of these compounds to reduce the metastatic potential of tumor cells (Damaskos *et al.*, 2017).

A promising strategy, against breast cancer cells in vitro and in mouse models, includes the combination therapy using Vorinostat and other agents to improve the treatment efficacy (Schech *et al.*, 2015, Chiu *et al.*, 2016).

In the phase I clinical study, a total of 60 patents (26 with Diffuse large B-cell lymphoma (DLBCL), 21 with Hodgkin lymphoma, 8 with T-cell lymphoma and 5 with B-cell lymphoma) were treated with Vorinostat-Gemcitabine- Busulfam- Melphalan in combination with Azacitidine (Nieto *et al.*, 2016). The overall survival rate resulted to be respectively 77% among the patients with DLBCL and 95% among those with Hodgkin lymphoma (Apuri and Sokol, 2016).

A phase IIb trial study evaluated the efficacy of Vorinostat in combination with lenalidomide and dexamethasone in 25 lenalidomide-refractory patients. The response rate was 24% and the clinical positive feedback rate was 80%. The most common reported adverse events of Vorinostat were nausea, fatigue, diarrhea and only 6% of the patients experience more severe side effects (Sanchez *et al.*, 2017).

Vorinostat has demonstrated promising effects against advanced leukemias, solid tumors, glioblastoma multiforme and further investigation of its profile is underway (Golabek *et al.*, 2015; How *et al.*,2015; Singh *et al.*, 2015; Stahl *et al.*, 2016, Montalban-Bravo *et al.*, 2017; Reddy *et al.*, 2020).

In a phase II clinical trial, Vorinostat in combination with bortezomib and Dexamethasone was found to be effective in the treatment of patients with RRMM. (ClinicalTrials.gov Identifier: NCT00773838).

- ***Belinostat (PXD-101)*** is a hydroxamic acid-type HDACi with inhibitory activity towards class I, II and IV HDAC isoforms. It has been approved by FDA for the treatment of PTCL (Garmpis *et al.*,2019). The recommended dosage of belinostat for the treatment of PTCL is 1,000 mg/m^2 administered over 30 minutes by intravenous infusion once daily on days 1 to 5 of a 21-day cycle.

To date, phase I and II clinical trials have been conducted in patients with solid tumor and RRMM therefore, Belinostat results being well tolerated with minimal side effects such as diarrhea, nausea, fatigue and anorexia (Tandon *et al.*, 2016; ClinicalTrials.gov Identifier: NCT01273155). Meanwhile, the combination of various proteasome inhibitors, and HDAC inhibitors for the treatment of lymphoma, and PTCL in particular, is currently under evaluation (Sawas *et al.*, 2015).

A phase II clinical trial is also testing the clinical activity of Belinostat as a single agent applied in patients with advanced-stage thymus tumors (ClinicalTrials.gov Identifier: NCT00589290).

Phase I clinical trials, trying to prove the synergistic interactions of Belinostat with Volasertiv (for B and T-cell lymphomas) and Zidovudine (for ATL), are in recruiting participants phase (ClinicalTrials.gov Identifier: NCT02737046; ClinicalTrials.gov Identifier: NCT02875002).

The efficacy of Belinostat and Erlotinib combination is underway phase II clinical trials in patients with non-small cell lung cancer (ClinicalTrials.gov Identifier: NCT0118870).

Another phase I study demonstrated the synergic effect of the combination of Belinostat and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in a group of 23 patients with PTCL. The observed overall response rate was 89%. The most adverse events were reported when CHOP were administrated alone (Johnston *et al.*,2021).

The safety and efficacy of Belinostatin combination with Bortezomib, was also tested in patients with RRMM, but considering the observed dose-limiting toxicity, the study was terminated in the Phase II trial (ClinicalTrials.gov Identifier: NCT00431340).

- ***Panobinostat (LBH-589)*** is a class I and II HDACi agent approved by the FDA for the treatment of CTCL and PTCL and in combination therapy with other agents in RRMM (Prebet and Vevy, 2011). Panobinostat is a hydroxamic acid HDAC inhibitor with high potency.

The antitumor activity of Panobinostat is associated with the induction of angiogenesis, induction of apoptosis and autophagy (Ganai, 2016).

Phase I clinical trials are investigating the combination of Panobinostat and Letrozole for the treatment of metastatic breast cancer. The recommended and tolerable dose for this co-treatment is; Panobinostat at 20 mg (oral route) three times a week administration and Letrozole at 2,5 mg daily. Researchers found that Panobinostat was able to prevent the growth of aromatase inhibitor-resistant cells establishing the innovative role of this compound in the treatment of metastatic breast cancer (Tann *et al.*, 2016).

The efficacy of Panobinostat in inhibiting breast cancer growth and metastasis in mouse models via up-regulating APLC expression, was recently demonstrated (Qin *et al.*, 2019).

A study conducted by Lee *et al.*, reported that the combination therapy Bortezomib/Panobinostat and Docetaxel showed better inhibition efficacy of tumor growth in cell line xenograft models in comparison with single treatment (Lee *et al.*, 2018).

The combination therapy of Panobinostat and proteasome inhibitors for the treatment of relapsed or/and refractory MM appear to be effective and well tolerated (Liu *et al.*, 2016).

A phase I clinical trial aiming to prove the possible treatment benefits in patients with RRMM, by combining Panobinostat with daratumumab, bortezomib and dexamethasone, is in recruiting participants phase (ClinicalTrials.gov Identifier: NCT04956302).

Encouraging results in terms of efficacy were observed, in phase III clinical trial, in which the combination therapy of Panobinostat with bortezomib and dexamethasone, was applied to RRMM patients. Researchers found that the co-treatment was able to reduce cancer size in 59% of the patients (ClinicalTrials.gov Identifier: NCT01023308). The most common side effects include; stomach pain, confusion, headache, loss of appetite, nausea and vomiting.

For the time being, clinical studies are in progress to evaluate the efficacy of Panobinostat in combination with other agents for the treatment of different type of cancer.

- ***Romidepsin (FK228)*** chemically belongs to the class of depsipeptides. It is a highly selective class I HDAC agent, approved by the FDA in 2009 for the treatment of CTCL and in 2011 for the treatment of PTCL (Valdez *et al.*,2015). The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.

At present time, Romidepsin is being considered a potential strategy mainly for the treatment of T-cell lymphomas, but also for hematologic and solid malignancies (Chun, 2015; Cacabelos and Teijido, 2018).

The combination Romidepsin- Alisertib is in phase I clinical trial for the treatment of relapsed/refractory aggressive B and T lymphomas (Strati *et al.*, 2020).

Wu*et al.* (2016) evaluated the combinatory effect of Romidepsin with Temozolomide (TMZ) in glioma cell lines, observing a significant level of apoptosis in glioma cells. Furthermore, in mice models, it was confirmed that the co-treatment, FK228 – TMZ is much more effective compared to each drug alone.

The potential anti-cancer activity of this agent in endometrial carcinoma, has been investigated by Li *et al.* in a study in which, the ability of Romidepsin in inducing tumor cell proliferation arrest at G0/G1 phase and apoptosis, was confirmed (Li *et al.*, 2016).

Falchi *et al.* in a phase I trial, found that the combination of oral 5-azacytidine and romidepsin, among 25 patients with relapsed/refractory PTCL, resulted to be safe and effective, with an overall response rate of 61% (Falchi *et al.*, 2021).

Promising efficacy results for CTCL patients were demonstrated in a phase I trial study, conducted by Vu *et al*. A combined therapy of romidepsin and liposomal doxorubicin was administered to 11 patients with CTCL and 12 patients with PCTL and the overall response rate was 60% and 27% respectively (Vu *et al.*, 2020).

Many clinical trials are evaluating the therapeutic combination benefits of Romidepsin- Azacitidine, Oxaliplatin, Gemcitabine, Dexamethasone in various lymphoid malignancies (ClinicalTrials.gov Identifier: NCT01846390; Yamaski *et al.*, 2019, Reiman *et al.*,2019).

Romidepsin is also being investigated in phase I/II trials as a novel drug in the cure of human immunodeficiency virus infection **(**ClinicalTrials.gov Identifier: NCT02092116**;** Mc Mahen *et al.*, 2020; ClinicalTrials.gov Identifier: NCT02616874; ClinicalTrials.gov Identifier: NCT02850016). The most common side effects observed were; stomach pain, confusion, headache, loss of appetite, nausea and vomiting.

Additional clinical studies using HDACi in combination therapy for pancreatic, breast and non/small cell lung cancer are in progress (Yao *et al.*,2015).

Considering all the data we reviewed for the above-approved HDACi, the current clinical results are promising, and they support the potential use of these compounds (as single agents and in combination regimens) for the treatment of a variety of malignancies.

4. DISCUSSION

The goal of this study was to investigate the recent progress toward the combination of approved HDACi with other chemotherapeutic agents in the treatment of a variety of tumors. In this review, we summarize the results of different clinical trials which could potentially lead the way to discover other HDAC inhibitors with greater therapeutic relevance.

Our findings suggest that the use of HDACi in combinatory anticancer regimens is considered a successful strategy in terms of lower toxicity and better clinical outcomes. Nevertheless, gathering more information relative to the higher safety doses, children's response toward these novel therapies and long-term toxicity remains still a challenge (ClinicalTrials.gov Identifier: NCT04308330).

Despite evidence suggesting that combination therapy regimens are more effective, the clear demonstration of the molecular events that define the cumulative benefit remains moderately understood.

Following the promising outcomes of HDACi used in CTCL, PTCL, RRMM, and in a small number of hematological lymphomas, further investigation must be carried out to evaluate their safety and efficacy profile against solid tumors. Regarding this issue, previous studies conducted have shown that HDACi are more effective in hematological malignancies than in solid tumors, and the reason why is probably related to stability matters. Nevertheless, we found that HDACi combined with other anticancer drugs, are commonly being tested in several phase I/II clinical trials for solid tumors malignancies, including ovarian cancer (Yadav *et al.*, 2019; Janyst *et al.*, 2018).

We also found that a promising strategy against breast cancer includes the combination therapy using Vorinostat and Tamoxifene in patients with advanced ER-positive breast cancer who had been treated with hormonal therapy and chemotherapy before. Furthermore, combining Panobinostat with Letrozole, was found to prevent the growth of aromatase inhibitor-resistant cells in metastatic breast cancer (Tan *et al.*, 2016). As well, the efficacy of Belinostat and Erlotinib combination is underway clinical evaluation in patients with non-small cell lung cancer (ClinicalTrials.gov Identifier: NCT0118870).

In our analysis, we also noticed that despite the interesting advances in cancer therapy, HDACi are achieving success in many other pre-clinical and clinical trials for non-neoplastic diseases, such as Alzheimer's disease, metabolic disease, HIV infection, and multiple sclerosis. In particular, Romidepsin is under investigation in phase I/II trials as a novel drug in the cure of human immunodeficiency virus infection (McMahen *et al.*, 2020). A

deeper investigation of this approach although, requires larger-scale clinical trials in order to prove the full potential therapeutic benefits of these agents.

In addition, Ricolinostat (ACY-1215) and Citarinostat (ACY-241) are two experimental HDACi, which are being tested in Phase I/II clinical trials in patients with relapsed or relapsed/refractory multiple myeloma (ClinicalTrials.gov Identifier: NCT01583283; ClinicalTrials.gov Identifier: NCT01997840).

The development of dual inhibitors is another interesting approach that could be further evaluated, as they will lead to compounds with simpler pharmacokinetic, lower toxicity and more efficient clinical efficacy.

The overall future perspective for the use of HDACi in a variety of malignancies, looks promising. However, more information regarding life quality changes associated with the administration of these agents, should be forthcoming. Finally, the development of suitable predictive biomarkers is necessary in order to provide information on the probability of response to the therapy in future clinical trials.

5. CONCLUSION AND FUTURE PERSPECTIVES

The findings reported in this paper emphasize the role of HDACi, as innovative pharmacological treatments for anticancer therapies. They induce numerous anticancer effects such as growth arrest, differentiation and in some cases cell death by apoptosis. Especially their significant synergistic effect with other conventional chemotherapeutic agents, has shown very promising results in clinical trials, ensuring high therapeutic efficacy, improvement of the clinical conditions and a reduction in side effects. However, a better comprehension of HDACi effectiveness and further evaluation of these anticancer agents is needed to optimize their efficacy, toxicity and overcome therapy resistance. Moreover, as most of these agents are broad-spectrum and nonselective, further research is required for the development of selective and more tolerable HDACi. Therapeutic strategies that include epigenetic drugs can therefore revolutionize the ongoing fight against cancer.

ABBREVIATIONS

CHOP - Cyclophosphamide, doxorubicin, vincristine and prednisone
CTCL -Cutaneous T-cell Lymphoma
DLBCL -Diffuse large B-cell lymphoma
ER+ -Estrogen Receptor-positive
FDA- Food and Drug Administration
HAT- Histone Acetyl Transferase
HDACi- Histone Deacetylase Inhibitors

HDACs- Histone Deacetylase enzymes
MM- Multiple Myeloma
PTCL -Peripheral T-cell lymphoma
RRMM- Relapsed/ Refractory Multiple Myeloma
SCFA – Short chain fatty acids

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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