Histone Deacetylase Inhibitors in the Treatment of Hematological Malignancies

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Abstract: Histone deacetylases (HDACs) play a central role in the epigenetic regulation of gene expression. Aberrant activity of HDACs has been found in several human cancers leading to the development of HDAC inhibitors (HDACi) as anti-tumors drugs. In fact, over the last years, a number of HDACi have been evaluated in clinical trials; these drugs have the common ability to hyperacetylate both histone and non-histone targets, resulting in a variety of effects on both cancer cells and immune responses. Clinical trials of HDACi conducted in solid tumors and hematological malignancies have shown a better clinical efficacy of these drugs in hematological malignancies. In this review, will be highlighted the mechanisms of action underlying the clinical responses obtained with these drugs and the doubts regarding the use of HDACi in cancer therapy.

Keywords: Histone deacetylases, histone deacetylases inhibitors, hematological malignancies.

1. INTRODUCTION

Epigenetic mechanisms such as DNA methylation, post-translational modifications of histone proteins and remodelling of nucleosomes affect chromatin structure and contribute to define heritable changes in gene expression. Therefore, histone acetylation represents one of many possible epigenetic modifications [1]. Histone acetylation regulates transcription by remodelling chromatin structure. Acetylations of the core histones disrupt the nucleosome structure, allowing unfolding and providing access for transcription factors to bind to their target promoters. The turnover of acetylation histones is regulated by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDCAs), where HATs allow transcriptions and HDACs repress transcription [2]. Deregulation of epigenetic mechanisms of gene expression may be as relevant as genetic alterations for the development and progression of cancer and leukemia.

In the eukaryotic cells, 18 different HDACs are identified and they may reside either in the nucleus or in the cytoplasm [3-4].

Class I family of HDACs consists of the 1, 2, 3 and 8 proteins; they are nuclear proteins, with homology to the yeast RPD3 protein, and are ubiquitously expressed in different human cell lines and tissues [5-6]. Class II family members include the 4, 5, 6, 7, 9 and 10 proteins; with homology to the Hda1 yeast protein [7]. They are able to shuttle between cytoplasm and nucleus. HDAC6 has unique substrate specificity with an α-tubulin deacetylase domains.

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The class III of HDACs comprises the so-called Sirts, consisting of seven members; these proteins, similar to Sirts in yeast, are zinc-independent and NAD-dependent [8].

Finally, HDAC class IV is constituted by a unique member, HDAC11, that share some features with HDAC class I and class II domains [9].

HDACs are mainly found associated with co-repressor proteins such as Sin3A, N-CoR and SMRT that are able to mediate their functions. HDACs are, in turn, regulated by different mechanisms including post-translation modifications, protein-protein interactions and availability of cofactors required for their enzymatic activity [10].

Recently, it has been shown that the activity of the different HDACs encompasses also several additional substrates such as transcription factors, signal transcription mediators, DNA repair enzymes, chaperones and structural proteins [11-12]. Indeed, HDACs are mainly involved in several cellular processes including cell proliferation, cell migration, angiogenesis. The identification of HDAC substrates proteins, as p53, HSP90, E2F, pRb and BCL6, REL A and Annexin A1 [11-14] that are all implicated in cancer progression, suggests that in cancer cells the aberrant pattern of acetylation is also extended to all HDAC possible substrates.

Dysregulated HATs or HDACs activity has been found in several human cancers [15-16], suggesting that the HAT/HDAC balance could be a potential therapeutic target in human neoplastic diseases. Indeed, the results of several preclinical studies have been shown that different classes of HDACi were found to exhibit potent antitumor activity. In this regard, over the last years, a number of HDACi have also been evaluated in clinical trials; these drugs have the common ability to hyperacetylate both histone and non-histone targets, resulting in a variety of effects on both cancer cells and immune responses.

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To date, responses with single agent HDACi have been predominantly observed in advanced hematologic malignancies including T-cell lymphoma, Hodgkin lymphoma, and myeloid malignancies. Generally HDACi are well tolerated with the most common acute toxicities being fatigue, gastrointestinal, and transient cytopenias, showing the highest degree of sensitivity, in terms of clinical efficacy [17].

Important clinical efficacy results were only reported in cutaneous T-cell lymphoma (CTCL). Vorinostat (SAHA) and Romidepsin (FK-228) have been approved for the treatment of these patients. However, in other cancers a variable and general insufficient clinical response suggesting that some questions remain to be clarified about their preferential activity in specific cancer types.

This review focuses on the clinical relevance of HDACi in hematological malignancies, and summarizes the results obtained in the clinical studies by HDACi and their mechanisms of action.

2. ROLE OF HDACs IN THE DEVELOPMENT OF HEMATOLOGICAL MALIGNANCIES

In both leukemia and lymphoma an abnormal activity of HATs and HDACs resulting in aberrant gene transcription, has been shown [18]. Furthermore, several HDACs are believed to be implicated in mediating the function of fusion proteins derived from oncogenic translocation of different forms of hematological malignancies [19].

Acute Promyelocytic Leukemia (APL) is caused by from the fusion between the product of promyeolocytic leukemia protein (PML) gene and the retinoic acid receptor-α (RAR-α).

RAR α, a ruling controller of myeloid differentiation, heterodimerizes with retinoid X receptors (RXR) and functions as a transcription repressor that, in the absence of retinoic acid, binds to specific DNA sequences of the HDACs coding genes (the RA responsive elements or RARE). Physiological levels of RA are however able to determine a conformational switch that leads to the release of the HDAC co-repressor complex and to the binding of RAR to a transcriptional activator, thus resulting into the transcription of RARE genes [20]. In APL, the aberrant recruitment of co-repressor complexes, PML-RAR is no more sensitive to physiological concentrations of RA, with the final outcome of silencing RAR-α target genes inducing differentiation block at the promyelocytic stage [21].

Acute myeloid leukemia subtype M2 is characterized by the presence of the fusion protein AML1-ETO, derived from chromosomal translocation and represents another important example in which HDAC-dependent aberrant transcriptional repression is implicated in the development of leukemia [22]. It was found that the fusion partner ETO binds to the human homolog of the murine nuclear receptor corepressor (N-CoR). N-CoR, mammalian Sin3 (mSin3A and B), and histone deacetylase 1 (HDAC1) form a complex that is able to change chromatin structure and mediates transcriptional repression by nuclear receptors and by a number of oncoregulatory proteins. Moreover, it found that ETO, through its interaction with the N-CoR/mSin3/HDAC1 complex, is also a potent repressor of transcription [23]. There are many evidences that strongly support the involvement of HDACs in the development of AML [24-25]. Importantly, it has been shown that recruitment of HDACs is crucial to the repression of gene transcription caused by AML1-ETO. In fact, Valproic acid (VPA) treatment disrupts the AML1/ETO-HDAC1 physical interaction, stimulates the global dissociation of AML1/ETO-HDAC1 complex from the promoter of AML1/ETO target genes, inducing a significant antileukemic activity mediated by partial cell differentiation and caspase-dependent apoptosis. These data suggest the therapeutic use of HDACi in this form of leukemia.

HDAC-dependent abnormal transcriptional repression has been also implicated in non-Hodgkin's lymphomas. It has been shown that the translocations or mutations of the BCL-6 gene are the most common genetic abnormalities in non-Hodgkin's lymphomas [26]. BCL-6 is expressed at the highest level in germinal-centre of B cells and its expression is lost during terminal plasmacytic differentiation: it behaves as a transcriptional repressor associating directly and indirectly with class I and class II HDACs [27]. Acetylation has been identified as a mechanism to down-regulate BCL-6 activity by inhibiting the ability of BCL-6 to recruit complexes containing HDACs. HDACi treatment results in the accumulation of inactive acetylated BCL-6, leading to cell cycle arrest and apoptosis in B-cell lymphoma [28].

T-cell acute lymphoblastic leukemia (T-ALL) is a further example in which, the recruitment of HDAC1 containing repressor complexes by the overexpressed transcription factor SCL-TAL1 appears to be involved in the development of this leukemia. Translocation events resulting in the over-expression of the transcription factor SCL/TAL-1 have been found in up to 60% of cases in T-ALL [29]. SCL/TAL-1, through the recruitment of HDAC1 containing repressor complexes, interferes with the expression of genes important for thymocyte differentiation and survival [30].

3. HISTONE DEACETYLASE INHIBITORS IN THE TREATMENT OF HEMATOLOGICAL MALIGNANCIES

HDACi can be subdivided on the basis of both their chemical structure and selectivity profile. Regarding to the chemical structures of the HDACi tested in clinical trials, it is possible to identify cyclic peptides as FK228 (Romidepsin), benzamides as Entinostat (MS275) and Mocetinostat (MGCD103) and several hydroxamic acids. We report here the results of clinical studies on HDACi in hematological malignancies.

Hydroxamic Acids

3.1. Vorinostat (SAHA)

Vorinostat (N-hydroxy-N'-phenyl-octanediamide, formula C14H20N2O3) a member of the hydroxamic acid class (Table **1**), is a pan HDACs inhibitor. Indeed, it has been shown that inhibits class I and II HDACs, and causes apoptosis and cell cycle arrest in leukaemia cell lines *in vitro* [31-32].

Table 1. Classification of HDACi

HDACi class	Compounds	Chemical structure	Diseases	Clinical Phase	References
Hydroxamic acids	Vorinostat (SAHA)		Cutaneous T-cell lymphoma (CTCL)	approved	[36,37]
			Hodgkin/ non-Hodking lymphoma	II	[39]
	Belinostat (PXD101)		Refractory lymphoma	I	[44,45]
	Panobinostat (LBH589)		Cutaneous T-cell lymphoma (CTCL)	I	[50]
			Non-Hodking lymphoma	I	[51]
Cyclic peptides	Romidepsin (FK228)		Cutaneous T-cell lymphoma (CTCL)	approved	[57,58]
			Refractory CTCL	II	[59]
Benzamides	Mocetinostat (MGCD0103)		B-cell Lymphoma (DLBCL) Follicular lymphoma (FL)	II	[68]
	Entinostat (MS275, DX275)		Relapsed or refractory Hodgkin lymphoma	I	[73]

Several Phase I and II trials have confirmed the good safety profile, tolerability and single-agent activity of Vorinostat in patients with hematological malignancies [33-35]. Importantly, in a Phase II study of Vorinostat given on three different drug administration programs [400 mg once daily or 300 mg twice daily 3 days/week, or 300 mg twice daily for 14 days followed by a 7-day rest (induction) followed by 200 mg twice daily], to patients with refractory cutaneous T-cell lymphoma (CTCL), the response rate was 24%, showing that the 400 mg daily regimen had the most favorable safety profile [34]. In addition, a second Phase II trial in progressive or refractory CTCL reported an objective response rate of 30% [35]. In both studies, the most common adverse events were fatigue, nausea, diarrhoea and thrombocytopenia.

These studies led to the US Food and Drug Administration (FDA) approval of Vorinostat in October 2006 for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or

recurrent disease on or following two systemic therapies [36-37].

Since Vorinostat has been shown to induce clinical response in approximately 30% of patients with CTCL, it is very interesting to clarify the mechanism of action of Vorinostat in CTCL and to identify biomarkers predictive of Vorinostat response in this cutaneous lymphoma. The signal transducer and activator of transcription (STAT) signalling pathway was evaluated in a related study, showing that persistent activation of STAT1, STAT3, and STAT5 correlates with resistance to Vorinostat in lymphoma cell lines. Immunohistochemical analysis of STAT1 and phosphorylated tyrosine STAT3 (pSTAT3) in skin biopsies obtained from CTCL patients enrolled in the Vorinostat phase IIb trial, showed that nuclear accumulation of STAT1 and high levels of nuclear pSTAT3 in malignant T cells correlate with a lack of clinical response. These results suggest that deregulation of STAT activity plays a role in Vorinostat resistance in CTCL, and that strategies able to block this pathway may improve Vorinostat response. Furthermore, these findings may be of prognostic value in predicting the response of CTCL patients to Vorinostat. [38].

Vorinostat was also tested both in Hodgkin and in non-Hodgkin lymphoma patients [39]. In a Phase II study, in non-Hodgkin lymphoma (NHL), oral administration of Vorinostat at a dose of 200 mg twice daily on days 1 through 14 of a 21-day cycle until progression or unacceptable toxicity. The median number of Vorinostat cycles received was nine. Vorinostat induced complete response in 4 patients and partial response of the 17 patients enrolled with relapsed/refractory follicular lymphoma (FL) in this study. The drug was well-tolerated over long periods of treatment, with the most common grade 3 adverse events being thrombocytopenia, anemia, leucopenia, and fatigue.

Patients with relapsed or refractory leukemias or myelodysplastic syndromes (MDS) represent other hematological malignancies in which Vorinostat has been studied [40]. A phase 1 study was conducted to evaluate the safety and activity of oral Vorinostat 100 to 300 mg twice or thrice daily for 14 days followed by 1-week rest. Of 41 patients, 31 had acute myeloid leukemia (AML), 4 chronic lymphocytic leukemia, 3 MDS, 2 acute lymphoblastic leukemia, and 1 chronic myelocytic leukemia. The most common toxicities were gastrointestinal (diarrhoea, nausea, anorexia, and vomiting) and fatigue. There were no drug-related deaths; only 7 patients had hematologic improvement response, including 2 complete responses and 2 complete responses with incomplete blood count recovery (all with AML treated at/below MTD). Acetylation of histone H3 was rapidly induced 2- to 3-fold in all patients evaluated regardless of dose level or response.

3.2. Belinostat (PXD101)

Belinostat [(2E)-3-[3-(anilinosulfonyl)phenyl]-N-hydroxyacrylamide, molecular formula C15H14N2O4S] is hydroxamic acid derivative, with activity versus class I and II histone deacetylases (Table **1**) [41].

Belinostat anticancer effect is thought to be mediated through multiple mechanisms of action, including inhibition of cell proliferation, induction of apoptosis, inhibition of angiogenesis, and induction of differentiation [42-43]. The compound has been shown to increase both the production of tissue inhibitor of metalloproteinase-1 (TIMP-1) and p21 expression in prostate cancer and to decrease the expression of potentially oncogenic proteins (mutant p53 and ERG) [43].

A phase I trial, in which Belinostat was administered by intravenous on days 1-5 in a cycle of 21 days in patients with advanced hematological neoplasia, indicated an acceptable safety profile [44]. The most common treatment-related adverse events (all grades) were nausea (50%), vomiting (31%), fatigue (31%) and flushing (31%). No grade 3 or 4 hematological toxicity compared with baseline occurred except one case of grade 3 lymphopenia.

Another clinical trial in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) or Hodgkin's disease (HD), in which Belinostat was administered by the oral route on days 1-14 every 3 weeks, has reported an acceptable safety profile [45].

Final Results of a Phase II Trial of Belinostat (PXD101) in patients with recurrent or refractory peripheral or Cutaneous T-Cell Lymphoma, in wich Belinostat was administered by intravenous on days 1-5 in a cycle of 21 days, showed a complete response in 24% in patients with PTCL and 14 % in patients with CTCL [46]. Hematological toxicity was minimal without any grade 4.

3.3. Panobinostat (LBH589)

Panobinostat [(2E)-N-hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl] acrylamide, molecular formula C21H23N3O2] is an hydroxamate analog with HDAC inhibitor (Table **1**). The compound has been shown to induce acetylation of H3 and H4 histones, to increase p21 levels, to disrupt the chaperone function of hsp90 and to induce cell-cycle G1 phase accumulation and apoptosis of K562 cells and acute leukemia MV4-11 cells [47].

Recently, LBH589 has been shown to induce apoptosis in Adult T-cell leukemia/lymphoma (ATLL)-related cell lines and primary ATLL cells and reduced the size of tumours inoculated in SCID mice. LBH589 was able to activate an intrinsic pathway through the activation of caspase-2. Furthermore, small interfering RNA experiments targeting caspase-2, caspase-9, RAIDD, p53-induced protein with a death domain (PIDD) and RIPK1 (RIP) indicated that activation of RAIDD is crucial and an event initiating this pathway. Interestingly, LBH589 caused a marked decrease in levels of factors involved in ATLL cell proliferation and invasion such as CCR4, IL-2R and HTLV-1 HBZ-SI [48].

A phase I trial, in which Panobinostat was administered by intravenous as a 30-minute infusion on days 1 to 7 of a 21-day cycle in patients with refractory hematologic malignancies, induced asymptomatic grade 3 Fredericia correction factor (QTcF) prolongations reported at the dose of 14mg/m2. Others potentially Panobinostat-related toxicities included nausea (40%), diarrhoea (33%), vomiting (33%), hypokalemia (27%), loss of appetite (13%), and

thrombocytopenia (13%) [49]. H3 acetylation increase was significant in B-cells $CD19^{+}$ and blasts $CD34^{+}$.

Similar results were obtained in the phase I study, with the "intravenous once a week" schedule in patients with non-Hodgkin lymphoma [50]. This trial represent the first evidence of Panobinostat clinical efficacy in CTCL and PTCL.

A phase I trial of oral Panobinostat, given for 3 days weekly on a 28-day cycle in patients with CTCL. This study reported that two cutaneous T- cell lymphoma (CTCL) patients achieved a complete response (5 and 7 months) and 4 CTCL patients attained a partial response (6.5, 8, 9 and 18+ months). The most common adverse events were anorexia, nausea, fatigue, diarrhoea and transient thrombocytopenia [51].

A phase II study of oral Panobinostat delivered for 3 days weekly in patients with refractory CTCL has enrolled 95 patients to date, with 15 patients achieved a complete response [52].

Preliminary results have been reported from a phase II study in which 38 patients with MM were treated with oral Panobinostat 20 mg MWF with modest results [53]

Cyclic Peptides

3.4. Romidepsin (FK228, Depsipeptide)

Romidepsin is a novel, natural, bicyclic tetrapeptide isolated from a broth culture of *Chromobacterium violaceum* (molecular formula C24H36N4O6S2). Formerly named FK228, Romidepsin bears the molecular structure of depsipeptides, namely sequences of alternating amino- and hydroxy-carboxylic acid residues. Romidepsin, (E)-(1S,4S,10S,21R)-7[(Z)-ethylideno]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23 tetraazabicyclo[8,7,6]-tricos-16-ene-3,6,9,22-pentanone, (Table **1**) needs to be metabolized in cells to be active [54].

More investigations demonstrated that this agent also effectively inhibits HDAC in human tumor cell lines and inhibits predominately type I HDACs [55]. Subsequently, it has been demonstrated that depsipeptide promotes apoptosis in both primary CLL and AML tumor cells *in vitro* at a concentration corresponding to that at which H3 and H4 acetylation and HDAC inhibition occurs [56].

However, similarly to other HDACi, an encouraging response has been observed in CTCL and in November 2009 Romidepsin was approved for the treatment of CTCL patients [57-58] for its tolerability and clinical efficacy in this malignancy.

Very recently, results from a multicenter international phase II study confirmed the efficacy of Romidepsin in patients with refractory cutaneous T-cell lymphoma (CTCL) [59]. The study was conducted in patients with stage IB to IVA CTCL who had received one or more prior systemic therapies and the response was determined by a composite assessment of total tumor burden including cutaneous disease, lymph node involvement, and blood. The response rate was 34% (primary end point), including six patients with complete response (CR). Twenty-six out of 68 patients (38%) with advanced disease achieved a response, including five CRs. The median time to response was 2 months whereas the median duration of response was 15 months. Drug-related adverse events were generally mild consisting mainly of GI disturbances and asthenic conditions. Nonspecific, reversible ECG changes were noted in some patients. In conclusion, the study demonstrated that Romidepsin has a significant and sustainable single-agent activity (including improvement in pruritus) and an acceptable safety profile, making it an important therapeutic option for treatment refractory CTCL.

Romidepsin has been investigated in several clinical trials involving patients with hematological malignancies such as CTCL and PTCL, AML, MDS, and MM [60-61].

Ten patients with CLL and 10 patients with AML were treated with 13 mg/m^2 depsipeptide intravenously days 1, 8, and 15 of therapy. Neither life-threatening toxicities nor cardiac toxicities were noted, although the majority of patients experienced progressive fatigue, nausea, and other constitutional symptoms that prevented repeated dosing. Limited antitumor activity has been generally reported since several patients had evidence of antitumor activity following treatment, but no partial or complete responses were noted by National Cancer Institute criteria [60].

Another clinical trial in patients with AML and MDS in which Romidepsin was administered one to five cycles of depsipeptide. The most common grade 3/4 toxicities were febrile neutropenia/infection (five patients), neutropenia/thrombocytopenia (nine patients), nausea (nine patients), and asymptomatic hypophosphatemia (three patients). No clinically significant cardiac toxicity was observed. The best response of 11 assessed patients was one complete remission in a patient with AML, stable disease in six patients, and progression of disease in four patients. Exploratory laboratory studies showed modest but rapid increases in apoptosis and changes in myeloid maturation marker expression. Histone H3 and H4 acetylation levels were evaluated in five patients; no consistent changes were observed [61].

Promising results have also been reported in phase II trial in PTCL patients, after Romidepsin administration as single agent [62]. Responses observed include 3 patients with CR and 7 patients with partial responses, yielding an overall response rate of 37%. Of note, responses were observed independent of stage of disease.

In a phase II Romidepsin trial in AML patients the anti-leukemic activity was only reported in patients with chromosomal aberrations encoding proteins known to recruit HDACs. Moreover, it has been reported a limited duration of the anti-leukemic activity probably due to the Romidepsin induction of MDR1 [63].

Romidepsin has been shown to exhibit antiproliferative and apoptotic effects against multiple myeloma cell lines. A phase II trial was performed of Romidepsin in patients with multiple myeloma who were refractory to standard therapy. Treatment was comprised of Romidepsin given as a 4-hour intravenous infusion on days 1, 8, and 15 every 28 days. Although no patients had an objective response, 4 of 12

patients with secretory myeloma exhibited evidence of M-protein stabilization, and several other patients experienced improvement in bone pain and resolution of hypercalcemia [64].

Benzamides

3.5. Mocetinostat (MGCD0103)

Mocetinostat (N-(2-aminophenyl)-4-[[(4-pyridin-3-ylpyrimidin-2-yl)amino]methyl]benzamide, C23H20N6O) (Table **1**) is an orally aminophenylbenzamide that selectively inhibits HDACs of class I and IV [65].

In B-cell chronic lymphocytic leukemia (CLL) cells from 32 patients, MGCD0103 has been shown to decrease the expression of Mcl-1, to induce translocation of Bax to the mitochondria, mitochondrial depolarization, and release of cytochrome c in the cytosol. Moreover, MGCD0103 treatment resulted in the activation of a caspase cascade downstream of caspase-9 [66].

Mocetinostat was studied in patients with refractory leukemia and myelodisplastic syndrome (MDS). Twenty-nine patients with a median age of 62 years were enrolled at planned dose levels (20, 40, and 80 mg/m^2. In this phase I study patients were treated with 3 times weekly schedule without interruption. The maximum tolerated dose was determined to be 60 mg/m^2, with dose-limiting toxicities (DLTs) of fatigue, nausea, vomiting, and diarrhoea observed at higher doses. Among the 29 patients evaluated for clinical response, three patients on the study achieved a complete bone marrow response at doses of 60 mg/m^2 and higher, suggesting a possible dose response at these. Interestingly, in the same study, Mocetinostat determined a dose dependent inhibition of HDAC enzymatic activity in patients' PBMCs (Peripheral Blood Mononuclear Cell) [67].

A phase II trial, in adults with relapsed or refractory diffused large B-cell Lymphoma (DLBCL) or Follicular Lymphoma (FL), demonstrated significant anti-cancer activity with manageable side effect profile. The most common toxicities were fatigue (14%), neutropenia (12%), thrombocytopenia (10%), and anemia (6%) [68].

In the Hodgkin lymphoma trial, Mocetinostat administration at the dose of 110 mg three times weekly, was able to achieve partial or complete remissions in the 35% of patients [69]. However this molecule has been removed by the FDA because of several cases of pericardial effusion in patients during the clinical trials. Beside the above reported side effects, the molecule showed, in general, the cluster of toxicities typical of other HDACi: gastrointestinal toxicity, fatigue and thrombocytopenia.

A phase II trial in Relapsed Follicular Lymphoma (FL), Mocetinostat administration at the dose of 110 mg three times weekly, showed that 19 patients (4.3%) with a pericardial serious adverse event (SAE) [70].

3.6. Entinostat (MS275, SNDX275)

Entinostat [pyridin-3-ylmethyl({4-[(2-aminophenyl) carbamoyl]phenyl}methyl)carbamate] (Table **1**) is a synthetic benzamide derivative that has been shown to preferentially inhibit the class I HDACs [71].

In vitro experiments with Entinostat demonstrated that this HDAC inhibitor has a dual anti-proliferative mechanism *via* down-regulation of XIAP and induction of apoptosis [72]. Furthermore, Entinostat may modulate the immune response by increasing interleukin-12, p40-70, IP10, and RANTES, and by decreasing the levels of IL-13 and IL-4, thus favouring Th1-type cytokines and chemokines. In addition, Entinostat induced the expression of a variety of tumour-associated antigens, including SSX2 and MAGE-A [72].

Clinical trial with this agent was first carried out in patients with advanced acute leukemias. DLTs included infections and neurologic toxicity such as unsteady gait and somnolence. Other frequent DLTs were fatigue, anorexia, nausea, vomiting, hypoalbuminemia, and hypocalcaemia [73]. Moreover, treatment with MS-275 induced increase in protein and histone H3/H4 acetylation, p21 expression, and caspase-3 activation in bone marrow mononuclear cells [73].

On the basis of this encouraging data, the safety and efficacy of Entinostat is currently being evaluated in a phase II multicenter study in patients with relapsed or refractory Hodgkin lymphoma. In this study, Entinostat is given 10 mg (two 5 mg tablets) orally, once every 2 weeks (days 1 and 15) in a 28-day cycle increasing to 15 mg in the absence of treatment related toxicity.

5. CONCLUSIONS

The results obtained from the clinical trials conducted with several HDACi in hematological malignancies indicate a clear clinical utility of these drugs in pathologies such as CTCL and PTCL.

Conversely, the clinical trials conducted in Hodgkin lymphoma and AML, although promising, still do not support the clinical utility of HDACi in these pathologies. In particular, anti-leukemic activity, although limited in time, was reported only in patients carrying translocation directly involving HDACs in the pathogenesis. This supports the concept of using HDACi in hematological malignancies characterized by a clear implication of HDACs in the development of leukemia.

The reason of the differential sensitivity between hematologic malignancies remains unclear. We believe that different reasons may explain these differences, such as the different expression of single HDACs. Important issues have still to be addressed, namely to verify the best profile of an HDACi in terms of selectivity toxicity and anticancer activity and to increase the data on the expression of HDAC/s in different hematological malignancies and in normal tissues.

Since some studies conducted during these trials showed a possible mechanism of resistance to HDACi, we also believe that identification of possible biomarkers could help to predict better clinical responses as well as possible causes of resistance.

Moreover, further studies will be needed to define adequate choices of dose and schedule since recent data indicate the importance of the individual optimization of these two parameters.

Finally, we think that a better use of HDACi for cancer therapy will be necessary to clarify the role of HDACs in both epigenetic and not epigenetic functions in order to understand the role of the whole acetyloma.

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