Histone deacetylase inhibitors in cancer therapy. A review

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Background. Despite recent success toward discovery of more effective anticancer drugs, chemoresistance remains a major cause of treatment failure. There is emerging evidence that epigenetics plays a key role in the development of the resistance. Epigenetic regulators such as histone acetyltransferases (HATs) and histone deacetylases (HDACs) play an important role in gene expression. The latter are found to be commonly linked with many types of cancers and influence cancer development. Overall, histone acetylation is being investigated as a therapeutic target because of its importance in regulating gene expression. This review summarizes mechanisms of the anticancer effects of histone deacetylase (HDAC) inhibitors and the results of clinical studies.

Results. Different HDAC inhibitors induce cancer cell death by different mechanisms that include changes in gene expression and alteration of both histone and non-histone proteins. Enhanced histone acetylation in tumors results in modification of expression of genes involved in cell signaling. Inhibition of HDACs causes changed expression in 2-10 % of genes involved in important biological processes. The results of experiments and clinical studies demonstrate that combination of HDAC inhibitors with some anticancer drugs have synergistic or additive effects.

Conclusions. Even though many biological effects of HDAC inhibitors have been found, most of the mechanisms of their action remain unclear. In addition, their use in combination with other drugs and the combination regime need to be investigated. The discovery of predictive factors is also necessary. Finally, a key question is whether the pan-HDAC inhibitors or the selective inhibitors will be more efficient for different types of cancers.

Key words: chromatin remodeling, histone acetylation, histone deacetylases, histone deacetylase inhibitors, combined treatment modalities, mechanisms of combined treatment

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INTRODUCTION

During the last few decades, several approaches have been applied in an effort to discover new more effective anticancer drugs. As a result, many promising compounds have been investigated. However, chemoresistance that may arise during chemotherapy is one of the main causes of failure of treatment. Epigenetic changes are emerging as part cause of the chemoresistence. These are the changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. They include changes in DNA methylation and chromatin remodeling, RNA transcripts and their encoded proteins, expression of non-coding RNAs, posttranslational changes in chromatin and mRNA regulation. Of these, histone acetylation and deacetylation have been investigated as therapeutic targets because of their importance in regulation of gene expression. Changes in histone acetylation influence chromatin condensation and these alterations influence gene transcription[1]. The balance between histone transacetylases and deacetylases is often damaged in cancer, leading to changed expressions of tumor suppressor genes and/or proto-oncogenes[1,2].

Enzymes catalyzing histone acetylation and deacetylation

Modification of histones by acetylation affects transcription by changing the structure of chromatin that modulates the accessibility of transcription factors to their target DNA and it plays an important role in regulation of expression[3]. Additionally, acetylation and/or deacetylation of non-histone proteins modify many important cell functions[4].

The acetylation state of histones and other proteins is maintained by histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes. HATs catalyze the transfer of an acetyl group from acetyl-CoA to lysine residues in proteins and HDAC removes it[5]. Depending on the mechanisms of removing the acetyl group, HDACs can be divided into two distinct families. The "classical family" comprises Zn^{2+}-dependent HDACs, the second family of HDACs depends in catalysis on NAD^{+} and subsequently, *O*-acetyl-ADP-ribose and nicotinamide are formed as a result of the acetyl transfer[6]. Furthermore, based on the homology to their yeast analogues, HDACs are divided into four classes. Class I, located in the nucleus, includes HDACs 1, 2, 3 and 8. HDACs 4, 5, 7 and 9 are members of class IIa, while isoforms 6 and 10 that are located both

in the cytoplasm and nucleus are classified as class IIb of HDACs. Class IV, which exhibits features of class I and II, includes only HDAC11. NAD^+-dependent homologues 1-7 of the yeast Sir2 proteins (sirtuins) are designed as class III of HDACs, and have mono-ADP-ribosyltransferase activity. HATs, "functional opponents" of HDACs, are divided into Gcn5/PCAF *N*-acetyltransferases (GNATs) and MYST HATs. Although these two groups of HATs are the major enzymes catalyzing *N*-acetyltransferase activity, other proteins also exhibit this acetylase activity[7].

Histone deacetylases and cancer

HDACs class I and II levels vary in different cancer cells. HDAC1 is overexpressed in prostate and gastric cancers, where it signalizes poor prognosis, as well as in lung, esophageal, colon and breast cancers[8-10]. High levels of HDAC2 have been found in colorectal, cervical and gastric cancers[11,12]. In addition, HDAC3 is overexpressed in gastric, prostate and colorectal cancer[13], and high expression of HDAC1 and 2 correlates with reduced patient survival in colorectal carcinomas[14,15]. HDAC6 is highly expressed in breast cancer, HDAC8 is over-expressed in neuroblastoma cells and its overexpression correlates with metastasis and advanced stage of disease with poor prognosis. Expression of HDAC11 is increased in rhabdomyosarcoma[5,16,17]. miR-449 that targets HDAC1 was identified in prostate cancer[18] and in hepatocellular carcinoma low levels of miR-22, which targets HDAC4, correlated with poor prognosis[19]. Both diffuse large B-cell lymphomas (DLBCL) and peripheral T-cell lymphomas exhibit HDAC1, 2 and 6 overexpression[20], whereas Hodgkin's lymphomas display increased HDAC1, 2 and 3 levels[21]. In Waldenstrom macroglobulinemia, the upregulation of miR-9* results in HDAC4 and 5 dowregulation[22].

Class III HDACs play an important role in carcinogenesis. Some act as antioncogenes while others influence tumors by controlling the cell metabolism[22]. Decreased activities of HDACs are associated with suppressed tumor cell development and growth[23,24]. Moreover mutations of HDAC4 have been identified in breast cancer samples[25] and mutation of HDAC2 that cause protein truncation was found in human epithelial cancer cell lines[26].

Histone deacetylase inhibitors

The results from various studies indicate that HDAC inhibitors increase the anticancer efficacy of additional therapy modalities and they therefore would be very efficient in the clinic together with other anticancer treatment modalities including ionizing radiation and/or chemotherapy. For this reason, investigation of the clinical application of HDAC inhibitors has increased with over 490 clinical trials for cancer and a few for other diseases[27]. Namely, HDAC inhibitors have also be found to be effective for treatment of other diseases. Some HDAC inhibitors have antimalarial properties and are studied as new possible drugs for the treatment of malaria[28]. There is also some evidence that HDAC pan-inhibitors and HDAC III inhibitors possess anti-inflammatory effects in models of asthma[29].

Here, we describe HDAC inhibitors, the mechanisms of their actions and we discuss combination therapies with anti-tumor drugs. HDAC inhibitors may be both specific against only some HDACs (HDAC isoform-selective inhibitors) or against all types of HDACs (pan-inhibitors). They can be classified according to their chemical structure into four groups: 1) hydroxamic acids; 2) aliphatic acids; 2) benzamides; 4) cyclic tetrapeptides[1].

1) Hydroxamic acids trichostatin A (TSA), vorinostat (suberoylanilide hydroxamic acid, SAHA) which was approved by the FDA as the first HDAC inhibitor for the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL) (ref.[30]), belinostat (PXD-101) and panobinostat (LBH589) are pan-HDAC inhibitors.

2) The aliphatic acids [valproic acid (VPA), butyric acid and phenylbutyric acid] are only weak inhibitors of HDAC I and IIa (ref.[31]).

3) Benzamides that include entinostat (SNDX-275, MS-275) and mocetinostat (MGCD0103) are isoform selective inhibitors of HDAC I and mocetinostat inhibits also IV HDAC (ref.[32]).

4) The cyclic tetrapeptides, inhibitors of class I HDACs (romidepsin inhibits also HDAC 4 and 6), are cyclic hydroxamic acids containing peptides: romidepsin (depsipeptide, FK228, FR901228), apicidin and trapoxinand. Of these, romidepsin that was approved by the FDA and the EuMedicines Agency to treat CTCL and peripheral T cell lymphomas, is most effective[33]. It is a prodrug which is activated to a metabolite that chelates the zinc ions in the active center of the HDAC of class I (ref.[34]).

MECHANISMS OF HISTONE DEACETYLASE INHIBITOR-INDUCED CELL DEATH

Different HDAC inhibitors induce death of cancer cells by different mechanisms that include changes in gene expressions and alterations of both histone and non-histone proteins. Enhanced histone acetylation in a variety of tumors results in modification of expression of the genes involved in cell signaling. Inhibition of HDACs causes changed expression of approximately 2-10% of genes involved in several biological processes such as cell cycle arrest and apoptosis induction[35]. Many genes contributing to the regulation of the cell cycle and apoptosis were found to be modified by HDAC inhibition[36,37]. Moreover some HDAC inhibitors have antiangiogenic effects[38]. Mechanisms of actions of HDAC inhibitors are summarized in Fig. 1.

Histone deacetylase inhibitors, cell cycle arrest and differentiation.

The most important mechanism of cell cycle arrest induced by HDAC inhibitors seems to be increased expression of gene CDKN1A (p21) encoding the p21 protein that blocks the formation of dimers from cyclins and cyclin dependent kinases. This leads to arrest of the cell cycle and to induction of cell differentiation[39]. The expression of p21 is tightly controlled by the tumor suppres-

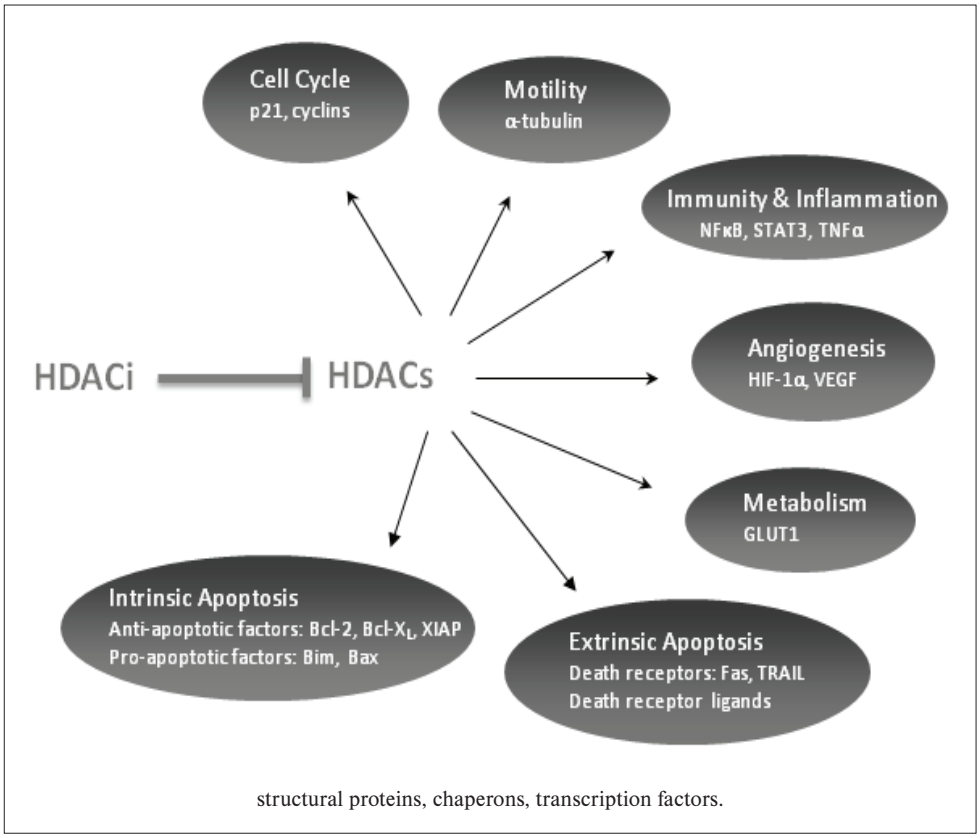

Fig. 1. Scheme of mechanisms of HDAC inhibitors action.

sor protein p53 that interacts with a Sp1 site of the p21 promoter, competing with HDAC1 which decreases transcription of p21 (ref.[40]). In cells treated with HDAC inhibitors, the HDAC1 protein is released from the Sp1 site, and this causes increase in p21 expression. Furthermore, HDAC inhibition stabilizes protein p53 by its acetylation[41]. Elevated acetylation of histones located close to the p21 promoter also facilitates the access of transcription factors. HDAC inhibitors can also repress expression of cyclins D and A (ref.[42]). For clinical practice, another important feature of HDACi which could find its place in cancer therapy, is regulation of cell differentiation through activation of ERK. VPA has been shown to enhance DNA binding and transactivation activity of the AP-1 transcription factor by ERK activation and acts as a potent inducer of differentiation of several types of transformed cells. It increases expression of c-Jun and c-Jun phosphorylation in SH-SY5Y neuroblastoma cells[43]. The latter feature is required to direct cellular differentiation of poorly differentiated PC12 rat pheochromocytoma cells[44].

Histone deacetylase inhibitors and apoptosis

HDAC inhibitors induce apoptosis in tumor cells by regulation of expression of proapoptotic and antiapoptotic genes[45]. Mechanisms by which different HDAC inhibitors induce apoptosis include activation of both extrinsic and intrinsic apoptotic pathways. HDAC inhibitors have been demonstrated to influence death receptors and their ligands[46]. HDAC inhibitor-induced apoptosis has also been demonstrated to be associated with activation of the intrinsic pathway[45]. It can be concluded that in tumor cells exposed to HDAC inhibitors proapoptotic genes involved in the extrinsic and intrinsic apoptotic pathways are up-regulated, while expression of antiapoptotic genes is reduced[12]. Moreover, increased reactive oxygen species (ROS) levels that induce apoptosis were found in cancer cells treated with HDAC inhibitors but not in nonmalignant ones treated by same drugs. Inhibition of caspases does not block HDAC inhibitor induced cell death. This means that HDAC inhibitors also induce non-caspase types of cancer cell death[47,48]. Two mechanisms responsible for induction of oxidative stress by HDAC inhibitors may be damage to mitochondria and modulation of cellular antioxidants[49].

HDAC inhibitors can also induce cell death in apoptosis resistant cells. One possible mechanism of non-apoptotic cell death induced by HDAC inhibitors is induction of autophagy. For example, FK228, an HDAC class I inhibitor and HDAC1 siRNA induce autophagy in HeLa cells *in vitro*[50]. SAHA caused tumor growth slowdown of glioblastoma xenografts in mice in which it induced autophagy. This HDAC inhibitor increased formation of intracellular acidic vesicle organelles, recruited LC3-II to the autophagosomes, potentiated Beclin1 protein levels and reduced p62. SAHA triggered autophagy through the downregulation of AKT-MTOR signaling. Inhibition of SAHA-induced autophagy by chloroquine has synergistic effects that further increase apoptosis[51].

Histone deacetylase inhibitors and cell signaling pathways

An important mechanism of the anticancer effect of HDAC inhibitors is regulation of cell differentiation by activation of some protein kinases [mitogen-activated protein kinases (MAPK), c-Jun Nterminal kinase (JNK) and p38] that modulate cell growth, differentiation and apoptosis. HDAC inhibitors increase expression of c-Jun and its phosphorylation in several cancer cells[43]. VPA and natrium butyrate also affect Wnt signaling that is important in various malignancies, by phosphorylation of glycogen synthase kinase-3β (GSK-3 β) (ref.[49,52]). HDAC inhibitors also induce the expression of some enzymes involved in the proteasomal degradation pathway[53].

Histone deacetylase inhibitors and angiogenesis and cellular stress response pathways

HDAC inhibitors can decrease angiogenesis by downregulation of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) (ref.[54]). VPA has been demonstrated to enhance expression of the antiangiogenic proteins thrombospondin-1 and activin A and to downregulate proangiogenic basic fibroblast growth factor[55]. We found that VPA and trichostatin A decrease formation of the capillary tubes of human vascular endothelial cells but they do not induce apoptosis of those cells (unpublished results). In addition, treatment of cells with HDAC inhibitors caused degradation of HIF-1α (hypoxia inducible factor), a proangiogenic transcription factor[56].

Hypocetylation of the chaperone Hsp90 protects its client proteins such as bcr/abl or ErbB2 from degradation[57]. In addition, hyperacetylation of Hsp90 induced by HDAC inhibitors reduces the chaperone association with its cancer-related client proteins, resulting in their proteasomal degradation[57].

COMBINATION OF HISTONE DEACETYLASE INHIBITORS WITH OTHER THERAPEUTIC REGIMENS

The results from in *in vitro* and *in vivo* experiments using various cancer cells have demonstrated that combination of HDAC inhibitors with a variety of anticancer drugs have synergistic or additive effects[58]. Chemotherapeutic combinations with HDAC inhibitors have also been used in clinical trials[59]. Several types of therapies have been investigated in combination with HDAC inhibitors.

1) HDAC inhibitors were combined with other epigenetic modifiers. Inhibitors of DNA methyl transferases 5-azacytidine (azacitidine) and 5-aza-2'-deoxycytidine (decitabine) had increased antitumor effects when used with HDAC inhibitors[60-64]. Decitabine and VPA both induced apoptosis and the combination increased their effects both *in vitro* and *in vivo*[65,66]. Co-treatment of prostate, pancreatic tumor, acute myelogenous leukemia (AML) AML1/ETO-positive and non small cell lung cancer (NSCLC) cells with trichostatin A and decitabine synergistically induced apoptosis[63,64,67,68]. In addition, an inhibitor of histone demethylases (tranylcypromine) and vorinostat showed synergistic enhancement of apoptosis in glioblastoma cells[45].

2) Promising results have been reported for combinations of HDAC inhibitors and ROS-generating agents. One such agent, adaphostin, increases entinostat and vorinostat induced apoptosis in leukemia cells[45]. In addition depletion of GSH, that is a ROS scavenger, increases the effects of vorinostat on AML cells[69].

3) Other drugs that have been combined with HDAC inhibitors are microtubule stabilizers. VPA increases the toxic effects of paclitaxel in anaplastic thyroid carcinoma cells due to their interaction with the tubulin β subunit. VPA enhances tubulin hyperacetylation that stabilizes microtubule structures[70]. Similar enhancement of apoptosis was observed in endometrial carcinoma cells treated with trichostatin A and paclitaxel caused by the activation of the intrinsic mitochondria-dependent pathway. Trichostatin A also stabilizes microtubules via α-tubulin acetylation both *in vitro* and *in vivo*[71].

4) Another effective combination of HDAC inhibitors is that with proteasome inhibitors. Cancer cell death due to a combination of proteasome and HDAC inhibitors is caused by induction of oxidative stress, endoplasmic reticulum (ER) stress and stimulations of JNK. Bortezomib, marizomib (NPI-0052) and carfilzomib are proteasome inhibitors which have been combined with HDAC inhibitors. Treatment of multiple myeloma cells with bortezomib made the cells more sensitive to vorinostat and sodium butyrate induced apoptosis[72]. Clinical trials of vorinostat in patients suffering from multiple myeloma demonstrated an increase in its antitumor effects in combination with bortezomib[73,74]. Mechanisms of the anticancer effects of a combination of proteasome and HDAC inhibitors are mitochondrial damage, disruption of aggresome formation, stimulations of JNK and caspases and enhancement of oxidative and ER stress[72,75]. Proteasome inhibitor, marizomib in combination with vorinostat or entinostat increased apoptosis in several leukemia cells, caspase 8 activation and oxidative stress contributed to the synergistic effects[45]. *In vitro* and *in vivo* studies with diffuse large B cell lymphoma and mantle cell lymphoma cells including bortezomib resistant ones showed that another proteasome inhibitor, carfilzomib, increased the effects of vorinostat[76,77].

5) Numerous studies show synergisms or additive effects combining the HDAC inhibitors and DNA-damaging agents such as topoisomerase inhibitors, DNA-intercalators, inhibitors of DNA synthesis and agents covalently modifying DNA (i.e. doxorubicin, epirubicin, etoposid, cisplatin, 5-fluorouracil, melphalan, and temozolomide and ionizing radiation in many cancer cell lines) (ref.[78]).

CLINICAL STUDIES AND REGISTERED DRUGS

Several HDAC inhibitors of different structural classes are under clinical development (see Table 1). These include the short-chain fatty acids (phenyl butyrate and val-

Table 1. HDAC inhibitors under clinical development.

Chemical structure	Name	HDAC specifity	Study phase
Hydroxamates	SAHA (vorinostat)	Pan-inhibitor	Approved for CTCL, phase III alone or in combination
	PXD101 (belinostat)	Pan-inhibitor	Phase II alone or in combination
	LBH589 (panobinostat)	Classes I and II	Phase III alone or in combination
	ITF2357 (givinostat)	Pan-inhibitor	Phase II alone or in combination
	4SC-201 (resminostat)	Pan-inhibitor	Phase II alone or in combination
	PCI 24781 (abexinostat)	Classes I and II	Phase II alone or in combination
Cyclic peptides	Depsipeptide/FK228 (romidepsin)	Class I	Approved for CTCL and PCTL, phase III alone or in combination
Benzamides	MS-275 (entinostat)	Class I	Phase II alone or in combination
	MGCD0103 (mocetinostat)	Class I	Phase II alone or in combination
Aliphatic fatty acids	Valproic acid	Classes I and IIa	Phase II alone or in combination (approved for epilepsy and some other nonmalignant disseases)
	Butyrate	Classes I and IIa	Phase II alone or in combination

proic acid); the hydroxamic acids [vorinostat (Zolinza®, SAHA); panobinostat (LBH589); PCI-24781 and belinostat (PXD101)]; the cyclic tetrapeptides [romidepsin (Istodax®, FK228); and the benzamides entinostat (MS-275)]. Two HDAC inhibitors, vorinostat and romidespin, have been approved by the US FDA for treating patients with progressive, persistent or recurrent cutaneous T-cell lymphoma (CTCL) after one or more lines of chemotherapy and romidepsin for patients suffering from peripheral T cell lymphoma who received at least one prior therapy[79,80]. Vorinostat had modest activity as a single-agent. Its response rate is 10-20% in AML and MDS patients. However this HDAC inhibitor, in combination with 5-azacitidine, increased response rate by 30%. The combination of vorinostat with idarubicin and cytarabine had synergistic activity that was maximal when vorinostat preceded cytarabine. In a phase II trial, the response rate of 85% of the combination was superior to that of idarubicin and cytarabine alone; notably, there were responses in all patients with FLT3-ITD mutations[81,82]. Phase II trials using administration of vorinostat in refractory cutaneous T-cell lymphoma patients showed an objective response in nearly 30% of these patients[30,83]. HDAC inhibitors also appear to be active in AML, lymphomas and myelodysplastic syndromes (MDS). Inhibition of HDACs mediates the epigenetic gene silencing in common translocations associated with certain hematological malignancies such as AML/ETO fusion protein[84]. Phase I study of patients with advanced leukemia and MDS treated with vorinostat showed clinical benefit in 17% (ref.[85]). The clinical phase II study proved that panobinostat is an active therapeutic agent in patients with relapsed/refractory Waldenström macroglobulinemia with a response rate of 47% (ref.[86]).

MGCD0103 (Mocetinostat) was evaluated in a clinical phase II trial for the treatment of patients with refractory chronic lymphocytic leukemia (CLL). This HDAC inhibitor alone showed only limited efficacy. For this reason, mocetinostat in combination with other agents such as conventional chemotherapeutic drugs was recommended[87]. LBH-589 (Panobinostat) underwent phase I and II clinical studies for the treatment of solid and hematologic maligancies and phase III clinical trials against CTCL and CML. Two phases I clinical trials showed promising results using LBH-589 in an oral and intravenous form against CTCL (ref.[88]) and leukemias, respectively[89]. Both studies found increased acetylation of histones in tumor cells that was associated with apoptosis. LBH-589 also underwent several phase III clinical trials against CTCL too and leukemia in its oral form and showed positive effect for the treatment of those diseases.

Despite promising results in the treatment of CTCL, vorinostat and romidepsin have not been effective in studies that involved solid tumors. Clinical trials have assessed their efficacy against different solid tumors, e.g. neuroendocrine tumors, glioblastoma multiforme, mesothelioma, refractory breast, colorectal, NSCL, prostate, head and neck, renal cell, ovarian, cervical and thyroid cancers. None of the patients included in these trials showed at least partial response to treatment and they suffered from side effects[27]. A study that assessed whether VPA modulates the efficacy of radiochemotherapy with temozolomide in glioblastoma patients showed that combined therapy with VPA was more effective over patients treated without HDAC inhibitors. The authors of this study reasoned that the improvement of in treatment results in the arm with VPA was due to the inhibition of HDAC (ref.[90]).

VPA with doxorubicin appeared to be an effective chemotherapy regimen (16% response rate) in patients with refractory or recurrent mesothelioma[91]. Vorinostat

enhanced the efficacy of carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer[92]. One clinical study showed that the combination of vorinostat and tamoxifen exhibited encouraging activity in reversing hormone resistance of breast cancer[93].

The most common side effects of HDAC inhibitors are thrombocytopenia, neutropenia, diarrhea, nausea, vomiting and fatigue. Most toxicities are not class-specific and have been observed in all HDAC inhibitors[94].

CONCLUSIONS AND FUTURE PERSPECTIVES

It is well known that various HDACs are involved in different pathways and functions in the cell. Nevertheless, additional studies are necessary to disclose other functions of HDACs and determine their cellular interactions. Such studies might result in development of more efficient therapy with HDAC inhibitors that are a promising group of anti-cancer drugs utilized either individually or in combination with other anti-cancer drugs. Of HDAC inhibitors, vorinostat and romidepsin have been approved for cutaneous T-cell lymphoma and romidepsin also for peripheral T-cell lymphoma. Many other HDAC inhibitors are in clinical trial for the treatment of both haematological and solid malignancies. Even though many biological effects of HDAC inhibitors have been found, explanations remain unclear. In addition, their use in combination with other drugs and the schedule of such drug combinations need to be investigated in detail. Indeed, recently, we have found that VPA increased the cytotoxicity of etoposide to neuroblastoma cells *in vitro*, if etoposide was co-cultivated with VPA but preincubation of these cells with VPA decreased the etoposide efficacy[95]. The discovery of predictive factor(s) is also necessary. Further, one of the most important questions in this field is whether the pan-HDAC inhibitors or the selective inhibitors will be more efficient in different types of cancers.

ABBREVIATIONS

AML, Acute myelogenous leukemia; CTCL, Cutaneous T-cell lymphoma; DLBCL, Diffuse large B-cell lymphomas; eNOS, Endothelial nitric oxide synthase; FDA, US Food and Drug Administration; FK228, Romidepsin; GNATs, GSK-3 β, Glycogen synthase kinase-3β; Gcn5/PCAF *N*-acetyltransferases; HAT, Histone acetyltransferase; HDAC, Histone deacetylase; HIF-1α, Hypoxia inducible factor; Hsp90, Heat shock protein 90; JNK, c-Jun N terminal kinase; LBH589, Panobinostat; MAPK, Mitogen-activated protein kinases; MDS, Myelodysplastic syndromes; MGCD0103, Mocetinostat; NPI-0052, Marizomib; NSCLC, Non small cell lung cancer; PXD-101, Belinostat; ROS, Reactive oxygen species; SAHA, Suberoylanilide hydroxamic acid; SNDX-275, Entinostat; TSA, Trichostatin A; VEGF, Vascular endothelial growth factor; VPA, Valproic acid.

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CONFLICT OF INTEREST STATEMENT

The authors state that there are no conflicts of interest regarding the publication of this article.

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