The Breast 43 (2019) 130–134

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

The role of histone deacetylase inhibitors in metastatic breast cancer

Bruna Zucchetti [a, b], Andrea Kazumi Shimada [b], Artur Katz [b], Giuseppe Curigliano [a, c, *]

[a] IEO, European Institute of Oncology IRCCS, Milan, Italy
[b] Hospital Sirio-Libanes, Sao Paulo, Brazil
[c] Department of Oncology and Hematology, University of Milano, Milan, Italy

ARTICLE INFO

Article history:
Received 7 November 2018
Accepted 3 December 2018
Available online 6 December 2018

Keywords:
Breast cancer
Epigenetic
Histone acetylation

ABSTRACT

Histone deacetylase inhibitors (HDACi) are a relatively new class of drug that plays an important role in the epigenetic and non-epigenetic regulation in cancer, inducing death, apoptosis and cell cycle arrest in cancer cells. Although HDACi are approved only for hematologic malignancies, there are several trials in the breast cancer setting with promising results. In this review, we summarize the latest studies with HDACi in breast cancer from the emerging data in the translational research until its possible applicability in the clinical practice.

Contents

1. Introduction

Epigenetic alterations, which refers to the regulation of gene expression via post-translational modification of chromatin structure without changes in the DNA sequence, plays an important role in the pathogenesis of cancer [1]. Acetylation, one of the main epigenetic modifications, is a key regulatory mechanism for chromatin and gene expression and it is regulated by opposing actions of two families of enzymes: Histone acetyltransferases (HATs) and Histone deacetylases (HDACs) [2].

The histone acetylation by HATs open the chromatin structure to facilitate the binding of transcription factors and, subsequently, gene transcription can occur. Deacetylation of histones by HDACs tightens their interaction with DNA, resulting in a closed chromatin structure and the inhibition of gene transcription [3]. As the imbalance in the histone acetylation/deacetylation status plays an important role in the cancer development, it's been some years that HDACs are promising targets for therapeutic interventions intended to reverse aberrant acetylation states in tumors.

Although hematologic malignancies are the main clinical targets for HDAC inhibitors (HDACi) with the FDA approval of Vorinostat for cutaneous T-cell lymphoma and Panobinostat for multiple myeloma [4], there are several trials testing these drugs for solid

* Corresponding author. Division of Early Drug Development for Innovative Therapy Co-Chair Cancer Experimental Therapeutics Program Department of Oncology and Hemato-Oncology University of Milan European Institute of Oncology Via Ripamonti 435, 20141 Milano T F .
E-mail address: giuseppe.curigliano@ieo.it (G. Curigliano).
URL: http://www.ieo.it/

https://doi.org/10.1016/j.breast.2018.12.001
0960-9776/

tumors, including lung, breast and prostate cancer. Investigations about abnormal histone acetylation modification in breast cancer focus on initiating molecular mechanisms in breast cancer development, identification of new biomarkers to predict breast cancer aggressiveness and the therapeutic potential of these drugs to restore histone acetylation to normal levels in the treatment of breast cancer [5].

HDAC inhibitors have been tested in all breast cancer subtypes as preclinical research to date supports that this class of drug is able to target breast cancer through several different approaches including relief of transcriptional repression with an impact in the epithelial-mesenchymal transition (EMT), reactivation of silenced estrogen receptor (ER) in hormone receptor-negative tumors, restoring the sensitivity of hormonal therapy in estrogen-positive tumor and modulate HER-2 expression [6]. Although in clinical studies HDACi have failed to show considerable anti-tumor activity as single agents in breast tumors [7], promising data are arising in the combination with other anti-cancer agents. In this review, we aim to describe the latest data about HDACi in the breast cancer treatment and their applicability from the translational research findings in the clinical practice.

1.1. The HDAC superfamily and HDAC inhibitors

It had been reported that 8–20% of genes are regulated by HDACi at the transcriptional level via their inhibition of the HDAC function on histone tails and that they also could target gene transcription through an indirect mechanism by inhibiting HDAC interactions with non-histone proteins as HDACs also acts on a variety of proteins in additions to histones, including transcription factors, enzymes and HDACs themselves. Thus HDACs, collectively, have multiple substrates and are regulated at multiple levels, including association with other proteins, chemical modifications and interaction with components of intracellular signaling pathways. To this point, HDAC inhibitors have emerged as a novel therapeutic group of drugs with promising anti-cancer activity [8].

There are 18 different HDACs in human cells, split into four classes. Eleven of these enzymes (class I, IIa, IIb and IV) have a very similar catalytic site and are the “classical HDACs”, which require zinc as co-factor. Class III HDACs refers to sirtuins, which is independent of zinc and dependent on NAD+. Class III are insensitive to all class of HDACi in clinical use [9]. In the breast cancer field, *in vitro* experience with breast cancer cells showed a specific epigenetic pattern of HDAC expression and mutation. For example, overexpression of HDAC1 has been reported in gastric and breast cancer cells and increased levels of HDAC6 have been reported to correlate with improvement in recovery and overall survival in patients with hormone sensitive breast cancer [10].

On the basis of their chemical structure, HDACi can be classified into four main different groups, including hydroxamates, cyclic peptides, aliphatic acids and benzamides. Furthermore, since HDACi do not inhibit all HDACs in the same extent, they may be grouped into pan HDACs inhibitors or class I-specific inhibitors [11].

The first natural product that was found to have HDAC inhibitor activity was Trichostatin A (TSA) in 1990. However, since the production of TSA is expensive and it showed toxicity in clinical trials, it is now mainly used as a reference compound for newly discovered HDACi [12]. Suberoyl anilide hydroxamic acid (SAHA), known as Vorinostat, has a structure analog of TSA, is the first FDA-approved HDAC inhibitor as a treatment for cutaneous T lymphoma [13]. Others HDACi and their clinical status of development as anti-cancer therapy can be found on Table 1.

2. HDACi and breast cancer treatment

2.1. Hormone positive HER2 negative metastatic breast cancer

For patients with tumors that over-express estrogen receptor (ER), hormonal therapy reduces the risk of recurrence and improves survival in patients with metastatic disease. In the specific scenario of metastatic breast cancer, the effectiveness of the hormonal therapy is limited by the development of resistance, arising in nearly 50% of the patients [14]. Many cellular changes have been suggested as underlying mechanism for *de novo* or acquired resistance to anti-estrogen therapy, which includes altered ER expression and ligand independence, down regulating tumor suppressor genes such as PTEN, aberrant signaling via PI3K/AKT/mTOR intracellular signaling pathway, cyclin D1 overexpression and alteration in gene expression secondary to epigenetic modifications [14,15]. Currently, much emphasis is being placed on developing novel

Table 1
Histone deacetylase inhibitors in clinical trials against cancer.

Structural Class	Name	HDACs inhibited	Clinical trial status as anti-cancer drugs
Benzamide	4SC-202	Class I	Phase I
	Chidamide (Epidaza HBI8000)	HDAC 1,2, 3, 10	Approved (China)
	CI994	HDAC 1,3	Phase III
	Entinostat (SNDX-275)	HDAC 1, 2, 3, 9	Phase III
	Mocetinostat (MGCD0103)	Class I	Phase II/I
Carboxamide	Abexinostat (PCI-24781)	Class 1, 2, 3, 6, 8, 10	Phase II
	Quisinostat (JNJ-26481585)	Pan	Phase II
Cyclic Peptide	Depsipeptide (Romidepsin)	Class I	Approved (US)
Hydroxyacrylamide	Resminostat	Pan	Phase II
Hydroxamic acid	Belinostat (PXD 101)	Pan	Approved (US)
	CUDC-101	Class I, II, EGFR, HER2	Phase I
	Givinostat (ITF2357)	Class I and II	Phase II
	Panobinostat (LBH589)	Pan	Approved (US)
	Pracinostat (SB939)	Class I, IIa, HDAC6, IV	Phase II
	SHP-141	Not available	Phase I
	Tefinostat (CHR-2845)	Not available	Phase I
	Tricostatin A	Class I, II	
	Vorinostat (SAHA)	Pan	Approved (US)
Isothiocyanate	Sulforaphane (broccoli)	Not available	Phase II
Short chain fatty acid	Pivanex (AN-9)	Class I, IIa	Phase II
	Valproic acid	Class I, IIa	Phase I/II

Inhibitors are classified according to their chemical structure. HDAC classes: Class I: HDAC 1, 2, 3, 8; Class IIa; HDAC 4, 5, 7, 9; Class IIb: HDAC 6, 10; Class III: SIRT1-7 (bot inhibited by HDACi), Class IV: HAC11. Source: ClinicalTrials.gov (NIH).

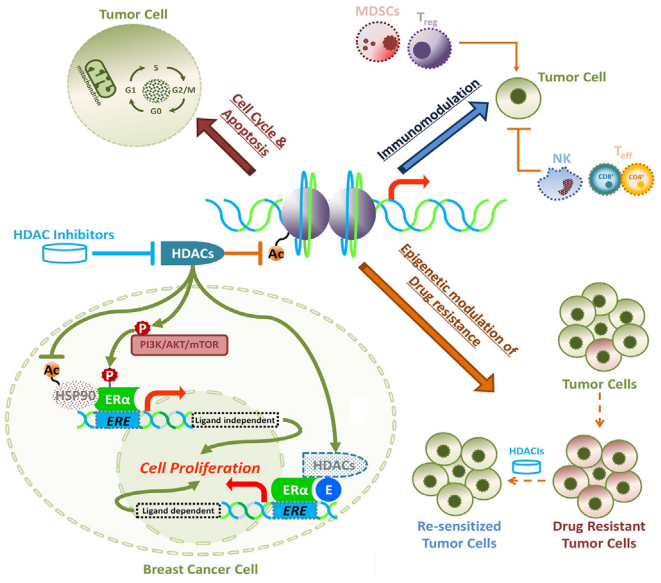

Fig. 1. Histone modulation and estrogen resistance: Histone modulation by histone deacetylases (HDACs) is a very important mechanism for epigenetic regulation, which is usually in dysfunction in tumor generally related to cell cycle and apoptosis, immunomodulation, and drug resistance. To estrogen receptor-positive breast cancer cells, HDACs are also involved in ER-mediated cell proliferation either in ligand-dependent or -independent mechanisms. Source: Phase III trial of chidamide, a subtype-selective histone deacetylase (HDAC) inhibitor, in combination with exemestane in patients with hormone receptor-positive advanced breast cancer – ESMO congress 2018. *Annals of Oncology*, Volume 29 Supplement 8 October 2018.

strategies to reverse hormone therapy resistance and HDACi have emerged as a promising new class of anti-cancer agents trying to restore the epigenetic alterations that led to hormonal resistance [16]. Fig. 1 illustrates histone modulation and estrogen resistance.

HDAC enzymes play an important role in the transcriptional regulation at the estrogen- and progesterone-mediated signaling pathway. At several points of this pathway, acetylation has been found to be a key mediator, regulating both the transcription and turnover of ER [17]. In fact, there are data in preclinical and clinical studies about the synergistic combination with HDACi and tamoxifen or aromatase inhibitor trying to reverse the hormonal resistance [14,18]. Preclinically, HDACi have shown to inhibit ER-positive tumor growth and restores hormone sensitivity as a result of down-regulation of estrogen-dependent growth factor signaling pathways, normalization of ERα levels and increase in aromatase enzyme levels [19].

Based on the previous knowledge of the synergistic effect of HDACi and anti-estrogen therapy, a clinical study conducted in China and presented by Z. Jian at the European Society of Medical Oncology (ESMO) congress this year – A phase III trial of Chidamide, a subtype-selective histone deacetylase inhibitor, in combination with exemestane in patients with advanced breast cancer (ACE trial), was the first phase III study to demonstrate benefit with HDACi in breast cancer (Fig. 1). The study enrolled a total of 443 postmenopausal woman with advanced breast cancer who progressed on endocrine therapy to receive, in a 2:1 randomization, Chidamide 300 mg biweekly + Exemestane versus Placebo + Exemestane. The study demonstrated improvement in the progression-free survival (PFS), which was the primary end point in the intention to treat (ITT) population by investigator assessment (PFS of 7.4 months for the Chidamide group X 3.8 months for the placebo group – HR: 0.775–95% CI, 0.582–0.978, p = 0,034). The overall survival (OS) data was still immature at the time of the cut-off date and had a median OS of 26.3 months for the placebo group (95% CI, 23.1 – NE) and non-evaluable on the Chidamide group. The most common adverse events were hematological toxicities – 81.6% of the patients presented neutropenia, although no febrile neutropenia was reported, 75% presented thrombocytopenia and 32% anemia. The investigators also reported that 25% of the patients presented hydroeletrolytic imbalance such as hypokalemia and 25% had nausea. An important data to point out is that from the 224 patients enrolled for the Chidamide group, 33.2% needed to reduce the dose of the medication and 48.4% had to interrupt the treatment for toxicity, which demonstrates that the side-effects are considerable. We still wait for the publication of this study and a more mature OS data [20].

Another example of the applicability of these researches in clinical practice is the ENCORE 301 study [21], a phase II randomized, placebo-controlled trial which evaluated the addition of the HDAC inhibitor entinostat to the steroidal aromatase-inhibitor exemestane in patients with ER-positive advanced breast cancer that had disease progression after prior treatment with a non-steroidal aromatase-inhibitor. The study demonstrated improvement in the progression-free survival, which was the primary end point (PFS HR 0.73, 95% CI 0.50 to 1.07, p = 0.06) and also in overall survival (OS, HR 0.59, 95% CI 0.36 to 0.97, p = 0,036).

The combination was well tolerated, with neutropenia (13%) and fatigue (11%) being the most frequent grade 3 or 4 toxicities in entinostat-treated patients. The promising results from the ENCORE301 trial led to FDA designation of entinostat as a Breakthrough Therapy for treatment of HR-positive advanced breast cancer when added to exemestane in postmenopausal women whose disease has progressed after nonsteroidal AI therapy.

In fact, the phase III study E2112 (Clinical-trials.gov NCT02115282) in now investigating exemestane in combination with entinostat/placebo in patients with locally advanced or metastatic breast cancer who have experienced disease progression after a non-steroidal aromatase inhibitor. ENCORE 301 also was able to demonstrate that HDAC inhibition leads to elevated protein lysine acetylation in tumor and peripheral-blood cells and, in an attempt to identify a predictive biomarker of response to the entinostat and exemestane combination, protein acetylation in peripheral blood mononuclear cells were evaluated at baseline and two weeks after commencement of entinostat and endocrine therapy. The median PFS was significantly longer in those patients with protein lysine hiperacetylation versus those who did not exhibit it (8.5 months versus 2.7 months, HR 0.32, 95% CI 0.13–0.79). According to this findings, elevated lysine acetylation in tumor and peripheral-blood cells might be a potential pharmacodynamics marker of the combination's activity.

2.2. Triple-negative metastatic breast cancer

Triple negative breast cancer (TNBC) represents a more aggressive subtype of breast cancer and, unfortunately, its treatment continues to be a clinical challenge because of its relatively poor prognosis, its aggressiveness and the lack of targeted therapies. Until now, the treatment for TNBC is based mostly on cytotoxic chemotherapy and, more recently, with PARP inhibitors and immunotherapy, but, despite the initial response to chemotherapy, resistance eventually develops in the majority of patients [22].

Giving the fact that epigenetic process control both the initiation and progression of TNBC [23], there is an increasing interest in the mechanisms, molecules and signaling pathways that participate in the epigenetic modulation of genes expressed in the carcinogenesis of TNBC, and so, the use of HDCAi for treatment of TNBC [24]. In fact, the loss of expression of E-cadherin responsible for the epithelial-mesenchymal transition (EMT) in basal-like subtype of TNBC is thought to be a result of an epigenetic silencing [25]. Also, there are

Table 2
Overview of the current trials ongoing with HDACi in breast cancer.

HDAC inhibitor	Combined drug	Condition	Stage o study
Entinostat	Exemestane	HR + metastatic BC	Phase III
Entinostat	Atezolizumab	TNBC metastatic	Phase II
Entinostat	Lapatinib + Trastuzumab	HER-2+ metastatic BC	Phase I
Entinostat	Prior surgery	TNBC Stage I-III	Early phase I
Entinostat	Ipilimumab + Nivolumab	Her-2 negative BC	Phase I
Belinostat	Direct tumor microinjection	Metastatic BC	Phase I
CUDC-101		Metastatic BC	Phase Ib
Panobinostat	PDR001 (Spartalizumab) +/− Everolimus	TNBC metastatic	Phase I
Depsipeptide	Cisplatin and Nivolumab	TNBC metastatic	Phase I/II
Depsipeptide	Single agent	Metastatic BC	Phase I

TNBC: Triple negative breast cancer; BC: Breast cancer; HR: Estrogen and/or progesterone receptor-positive BC, HER-2: Human epidermal growth factor 2.Source: ClinicalTrials.gov (NIH).

data showing that the ER-α loss in the TNBC is often related to an epigenetic alteration and when treated with Entinostat, ER-negative breast cancer cells have responded to aromatase inhibitors [26].

One of the new strategies for the treatments of TNBC is the use of immune checkpoint inhibitors, which has a rational as PD-L1 expression is found especially in HER-2 and triple-negative tumors. With the idea to enhance the immune response of TNBC, Terranova et al. [27] published a preclinical data with the combination strategy where Vorinostat, an HDACi, is applied with immune checkpoint inhibitors to improve immunotherapy responses in breast cancer. They found that Vorinostat up-regulated PD-L1 and HLA-DR on TNBC tumor cells and down-regulated CD4 Foxp3 Treg *in vitro*, leading to a significantly enhanced response to PD-L1/CTL4 blockade in TNBC mouse models, resulting in decrease of tumor growth associated with increased T cell tumor infiltration and reduction in CD4 Foxp3 T cells in the tumor microenvironment. In fact, applying clinically this rational that HDACis can enhance the immune checkpoint inhibitors response, there's a phase II trial in the recruiting phase with Atezolizumab (*anti*-PD-L1) and Etinostat (HDCAi) in TNBC (ClinicalTrials.gov identifier: NCT02453620).

HDACi are also known to induce apoptosis trough the regulation of various anti-and/or pro-apoptotic molecules such as Bcl-2 families molecules [28] and the mechanism underlying the suppression of Bcl-XL protein by HDAC inhibitors has been reported to be regulated at the transcriptional or translational level in several carcinomas, including TNBC. Although in theory, HDAC inhibitors seem to be promising anti-cancer drugs, their use as monotherapy is still limited for solid tumors and the trials testing them normally combine with another anti-cancer drug [29].

A recent study with the combination of a novel HDACi OBP-801 and Eribulin published by Ono H. et al. [30] showed that the combination had a synergistic inhibition of the grown in TNBC cells. The combination enhanced apoptosis as eribulin upregulated survivin and also HDACi could suppress the upregulation of survivin by eribulin. Moreover, this combination suppressed Bcl-xL and the MAPK pathway compared with either agent alone. These findings suggested that the combination might be a promising strategy for treating TNBC patients.

Another preclinical data using the HDAC inhibitors suberoylanilide hydroxamic acid (SAHA) or belinostat in TNBC is the combination with the PARP inhibitor (PARPi) Olaparib [31]. Although PARP inhibitors are shown to be especially aggressive to BRCA-mutated TNBC, some TNBC still remain resistant to PARPi as single agents [32]. The idea of combining HDACi and a PARPi is based on a previous knowledge that HDACi can decrease expression of proteins involved in the DNA repair, sensitizing TNBC to PARPi [33]. The combination of Olaparib and HDACi inhibited the proliferation of TNBC cell lines *in vivo* and *in vitro* with xenografts mouse models as the treatment relied on DNA damage-induced cell cycle arrest followed by the induction of apoptosis. The authors concluded that there's a rationale to this combination to reduce the homologous recombination efficiency in TNBC and sensitize TNBC tumors to the PARP inhibition.

2.3. HER-2 positive metastatic breast cancer

The treatment of HER-2 overexpressing tumors have improved in the past years using monoclonal anti-bodies (trastuzumab, pertuzumab and TDM-1) and small molecules (lapatinib and neratinib). However, despite to the initial response to the HER-2 blockage, resistance to HER-2 inhibitors frequently occur in the majority of patients and new strategies to overcome the resistant phenotype are needed [34]. The resistance to anti-HER2 drugs can be caused by the formation of heterotrimeric complex of HER-2 with both HER-3 and insulin-like growth factor-1 (IGF1) or activation of the PI3K-AKT-mTOR pathways [35].

Huang X et al. [36] demonstrated in preclinical models that SNDX-275, a class I HDAC inhibitor, could overcome trastuzumab-resistant in HER-2 breast cancer cells. SNDX-275 was able to re-sensitized trastuzumab-resistant cells and the combination of SNDX-275 plus trastuzumab enhanced trastuzumab induced growth inhibition in HER-2overexressing cells by a reduction of erb3 plus its phosphorylation (P-erb3) and inhibition of AKT signaling.

Lee J. et al. [37] showed, also in translational research, that entinostat combined with lapatinib synergistically inhibited proliferation and reduced *in vitro* colony formation resulting in *in vivo* tumor shrinkage or growth inhibition in two xenograft mouse models compared to each of the drugs alone. They proved that the anti-tumor activity of the combination was due to downregulation of phosphorylated AKT, which activated transcriptional activity of FOXO3, resulting in induction of pro-apoptotic proteins. They also demonstrated in this study that entinostat sensitized trastuzumab/lapatinib-resistance-HER2-overexpressing cells to the trastuzumab/lapatinib combination and enhanced the anti-proliferation effect compare with single agent or double combination treatment. This study provided evidence that entinostat has enhanced anti-tumor activity in combination with anti-HER-2 target therapy. To prove this hypothesis, there's a phase I clinical trial ongoing with entinostat in combination with lapatinib and trastuzumab for metastatic breast cancer previously treated with trastuzumab (Clinical-trials.gov identifier: NCT01434303). Table 2 summarize all studies ongoing with HDAC inhibitors in metastatic breast cancer.

3. Conclusions

It is very clear nowadays that histone acetylation modification plays an important role in the development of breast cancer and in the ability of cancer cells to become more invasive and resistant to

anti-cancer drugs. Between all the epigenetic treatments under development, HDAC inhibitors represent the first successful anti-cancer epigenetic therapy, especially for hematological malignancies. Although until now we have just one phase III trial demonstrating HDACi activity in breast cancer and it is not yet approved for clinical use apart from the hematological setting, they arise as a promising class of drug for the treatment of all breast cancer subtypes, especially for currently refractory hormone positive disease.

HDAC inhibitors represent also a potential combination therapy with other agents (as immune-checkpoint inhibitors) in patients with metastatic TNBC. Although much progress had been made in the HDACi field, it is still not completely clear how effective they are for solid tumors and our ability to identify the responding tumors is limited by our poor understanding of the mechanism that underlies its effectiveness.

Declaration of interest

The authors have declared no conflicts of interest.

Acknowledgements

Bruna Zucchetti acknowledges European School of Oncology for providing support for a fellowship at European Institute of Oncology.

References

[1] Zhang J, Zhong Q. Histone deacetylase inhibitors and cell death. Cell Mol Life Sci 2014;71:3885–901.
[2] Sterner DE, Berger SL. Acetylation of histones and transcription-related factors. Microbiol Mol Biol Rev 2000;64:435–59.
[3] Grustein M. Histone acetylation in chromatin structure and transcription. Nature 1997;389:349–52.
[4] Halsall JA, Turner BM. Histone Deacetylase inhibitors for cancer therapy: an evolutionary ancient resistance response may explain their limited success. Bioessays 2016;38:102–1110.
[5] Guo P, et al. Pathol Oncol Res 2018;24:807–13.
[6] Connolly R, Rudek M, Piekarz R. Entinostat: a promising treatment option for patients with advanced breast cancer. Future Oncol 2017;13:1137–48.
[7] Bots M, Johnstone RW. Rational combinations using HDAC inhibitors. Clin Canc Res 2009;15:3970–7.
[8] Glaser KB, Staver MJ, Waring JF, Stender J, Ulrich RG, Davidsed SK. Gene expression profiling of multiple histone deacetylase inhibitos: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. Mol Cancer Ther 2003;2:151–63.
[9] Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. Cold Spring Harb Perspect Biol 2014;6. a018712.
[10] Zhang Z, et al. HDAC6 expression is correlated with better survival in breast cancer. Clin Canc Res 2004;10:6962–8.
[11] Dokmanovic M, Marks PA. Prospects: histone deacetylase inhibitors: the next step? Biochim Biophys Acta 2005;1799:726–39.
[12] Tsuji N, Kobayashi M, Nagashima K, Wakisaka Y, Koizumi K. A new antifungal antibiotic trichostatin, J Antibiot 29:1-6.
[13] Mann BS, Johnson JR, Cohen MH, et al. FDA approval summary: Vorinostat for treatment of advanced primary cutaneous TY-cell lymphoma. Oncol 2007;12:1247–52.
[14] Thomas S, Thurn T, Raha P, et al. Efficacy of histone deacetylase and estrogen receptor inhibition in breast cancer cells due to concerted downregulation of akt. J Pone 2013.
[15] Mohla S, Stearns V, Sthyamoorthy N, et al. The biology of hormone refractory breast and prostate cancer: an NCI workshop report. Cancer Biol Ther 2009;8(21):1975–85.
[16] Yeruva SLH, Zhao F, Miller KD, et al. E2112: randomized phase III trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor positive advanced breast cancer – review article. NPJ Breast Cancer 2018;4:1.
[17] Thomas S, Munster P. Histone deacetylase inhibitor induces modulation of anti-estrogen therapy. Cancer Lett 2009;280:184–91.
[18] Raha P, Thomas S, et al. Combined histone deacetylase inhibition and tamoxifen induces apoptosis in tamoxifen-resistant breast cancer models by reversing Bcl-2 overexpression. Breast Canc Res 2015;17:26.
[19] Sabnis GJ, Goloubeva O, Chumsri S, et al. Functional activation of the estrogen receptor-α and aromatase by the HDAC inhibitor entinostat sensitizes ER-negative tumors to letrozole. Cancer Res 2011;71:1893–903.
[20] Abstract 283O_PR - phase III trial of chidamide, a subtype-selective histone deacetylase (HDAC) inhibitor, in combination with exemestane in patients with hormone receptor-positive advanced breast cancer – ESMO congress 2018. Ann Oncol October 2018;29(Supplement 8).
[21] Yardely DA, Ismail-khan RR, Melichar B, et al. Randomized Phase II, double-blinded, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J Clin Oncol 2013;31:2128–35.
[22] Gu G, Dustin D, Fuqua SA. Targeted therapy for breast cancer and molecular mechanisms of resistance to treatment. Curr Opin Pharmacol 2016;31:97–103.
[23] Garmpis N, Damaskos C, Garmpi N, et al. Histone deacetylases as new therapeutic targets in triple negative breast cancer: progress and promises. Cancer Genom Proteomic 2017;14:299–313.
[24] Marks DL, Olson RL, Fernandez-zampico ME. Epigenetic control of the tumor microenvironment. Epigenomics 2016;8:671–87.
[25] Trapani D, Esposito A, Criscitiello C, Mazzarella L, Locatelli M, Minchella I, Minucci S, Curigliano G. Expert Opin Investig Drugs 2017;8:965–71.
[26] Sabnis JG, Goloubeva O, Chumsri S, et al. Functional activation of the estrogen receptor and aromatase by HDAC inhibitor, entinostat sensitizes of ER-negative tumors to letrozole. Cancer Res 2011 March 1;17:1893–903.
[27] Terranova-Barberio M, et al. Oncotarget 2017;8(No. 69):114156–72.
[28] Johnstone RW, Licht JD. Histone deactylase inhibitors in cancer therapy: is transcription the primary target? Cancer Cell 2003;4:13–8.
[29] Wang L, Li H, Ren Y, et al. Targeting HDAC with a novel inhibitor effectively reverses paclitaxel in non-small cell lung cancer via multiple mechanisms. Cell Death Dis 2016;7. e2063.
[30] Ono H, Sowa Y, et al. The histone deacetylase inhibitor OBP-801 and eribulin synergistically inhibit the growth of triple negative breast cancer cells with the suppression of survivin, Bcl-xL and the MAPK pathway. Breast Canc Res Treat 2018;171:43–52.
[31] Marijon H, Lee DH, et al. Co-targeting poly-8ADP-ribose) polymerase (PARP) and histone deacetylase (HDAC) in Triple-negative breast cancer: higher synergism in BRaCa mutated cells. Biomed Pharmacother 2018;99:543–51.
[32] Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high grade serous or poorly differentiated ovarian carcinoma or triple negative breast cancer: a phase 2, multicenter, open-label, non-randomised study. Lancet Oncol 2012;12:852–61.
[33] Ha K, Fiskus W, Choi DS, et al. Histone deacetylase inhibitor treatment induces "BRCAness" and synergistic lethality with PARP inhibitor and cisplatin against human triple negative breast cancer cells. Oncotarget 2014;5:5637–50.
[34] Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted HER-2 therapy and personalized medicine. Oncol 2009;14:320–68.
[35] Valabrega G, Montemurro F, Angelietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER-2-overexpressing breast cancer. Ann Oncol 2007;18(6):977–84.
[36] Huang X, Wang S, et al. HDAC inhibitorSNDX-275 enhances efficacy of trastuzumab in erb-2 overexpressing breast cancer cells and exhibits potential to overcome trastuzumab resistance. Cancer Lett 2011 Aug 1;307:72–9.
[37] Lee J, Bartholmeusz C, Mansour O, et al. A class I histone deacetylase inhibitor, entinostat, enhances lapatinib efficacy in HER-2 overexpressing breast cancer cells through FOXO3-mediated BIM1 expression. Breast Canc Res Treat 2014;146(2):259–72.