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Review article

Role of Histone Deacetylase Inhibitors in Leukemia Therapy

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Abstract

Histone deacetylases (HDACs) are enzymes responsible for the deacetylation of both histone and non-histone substrates. They significantly impact gene expression by interfering with fusion genes and transcription factors, leading to the proliferation and migration of cancerous cells while inhibiting apoptosis through tumor suppressor genes. Evaluating the overexpression of HDACs in leukemias could offer a novel diagnostic strategy and reveal new therapeutic targets. Histone deacetylase inhibitors (HDACi) may reverse the activation of tumor suppressor genes (TSG), thus reducing the viability and malignant growth of tumor cells. A novel approach in HDACi designs involves the simultaneous inhibition of protein kinases and HDACs within a single molecule. The effectiveness of structurally varied compounds as HDAC inhibitors indicates that their mechanism of action might extend beyond merely obstructing the catalytic site, potentially involving interactions with the enzyme's rim and other proteins, independent of deacetylase activity. The efficacy of HDACi treatment has been validated in multiple clinical studies. Advancements in the discovery of new HDIs that target various cellular pathways could lead to innovative treatment options and improved survival rates for patients. This review focuses on the role of HDACs as therapeutic targets in different leukemia types.

Keywords: *Histone Deacetylase Inhibitors, Target, Overexpression, Tumor Suppressor Genes.*

Introduction

The major characteristics hallmark of tumorigenesis is deregulated cell proliferation and loss of cell differentiation [1]. Recent medical trails have been found the importance of genetic treatments which consider very effective in the most malignant diseases. For instance, by using epigenetic modifications principle as therapeutic agent against wide range of neoplasm and cancer; an alteration in gene expression without a change in the nucleotide sequence [2]. These epigenetic changes can be influenced by either changes in the chromatin structure of DNA, chromatin remodelling caused by post translational modification in histones [3]. Or by DNA methylation of specific C (Cytosine) in promoters; promoter can be characterised as a region or part of the DNA which is located upstream the gene, its function to facilitating the transcription stage. Moreover, the methylation of DNA occurs in specific cytosine in the CpG Island promoters during the expression of genes [4, 5]. DNA methylation is simply defined as the process of the addition of a methyl group to the fifth carbon atom in the cytosine ring of the CpG dinucleotides [4]. CpG Island is associated with the 5-regulatory region of all housekeeping genes and genes those are widely expressed of about 40% of genes which are expressed in a tissue specific manner. While the majority of CpG located outside CpG Island are Methylated.CpG Island have methylated very low amount of mentholated CpG, unmethylated CpG island (promoter, regulatory region) require for gene transcription [5, 6]. It is a mechanism for switch off gene transcription, this process is considered as epigenetic phenomena which lead to change in the gene expression without alteration in the bases sequence, the enzyme which is responsible for this process is known as DNA methyltransferase [7]. DNA methyltransferase is a family of enzymes which catalyses the transfer of a methyl group from S-adenosyle methionine to cytosine is CpG of the DNA [4]. There are different types of DNA methyltransferase such as, DNMT1, DNMT2, DNMT3a, and DNMT3b [7]. The most common type is the mammalian DNMT1 which has hemimethylated property, in addition to its ability to performing de novo methylation (totipotent of embryogentic stage) of unmethylated substrates in vitro [4]. Methylation plays an important role in modifying gene expression, surprisingly has a major impact on carcinogens. Many medical trails have been found that carcinogenic cells show aberrant in the DNA that is resulting from both histone post-translation modification and DNA methylation

in turn have affect on the chromatin structure [8]. By using such an efficient strategy leads to make new powerful therapeutic weapon against several haematopoietic malignancies.
Many studies have been performed studies on the effect of targeting tumours by using the strategy of the DNA methylation [9]. For instance, the clinical trials which are performed on some cases of patients who are suffered from chronic lymphoid leukaemia CLL. CLL is a tumour cell appears to be a relatively mature B cell with weak surface expression of Immunoglobin IgM or IgD [10]. Furthermore, the aetiology of CLL is idiopathic and the life expectancy is short in the most cases. It has been found that most CLL cases shown diminishing in the DNA methylation levels although there are a few exception in some cases which demonstrate hypermethylation by using high throughput capillary electrophoresis [11]. However, by applying another technique which is known as Restriction landmark genomic scanning (RLGS) with patients who have acute myeloid leukaemia have shown elevated in methylation level. In addition to, "the differences in the amount of aberrant methylation in comparison to normal bone marrow. Moreover, the process of the DNA methylation occurs in non-random distribution manner" [11]. The successful identification is by using the epigenetic alteration phenomena in attempt to cure a broad spectrum of malignancies particularly the role of histone deacetylase inhibitors as anti-carcinogenic agent specifically in haematopoietic malignancies. Moreover, it's combination with other drugs which show optimistic and promising outcomes in the drug development for human cancer therapy. However; there is still ambiguity or some fundamental aspects not fully understood.

Structure of histone

Histone is the combination of both DNA and proteins which consider the building block of chromatin that has a positive charge attributed to presence of lysine and arginine that neutralised the charge of DNA [12]. There are five types of histone which known as H1 that exist in linker form and two molecules of each H2A, H2B, H3 and H4 which are located in the core [13]. Several reports have demonstrated that both H2A and H2B are capable to moving easily, therefore enable the chromatin fibre to open and as consequence the transcription process occurs, next diagram shows the types of histone and how the transcription occurs [14]. Furthermore, Histones undergo several post-translational modifications such as, acetylation, methylation, phosphoralation, ubiquitylation and sumoylation [9]. These modifications can occur either at the tail region of N-terminal histone or within the globular domain of histones [15].Theses modifications have been identified by specific antibodies or by mass spectrometry.

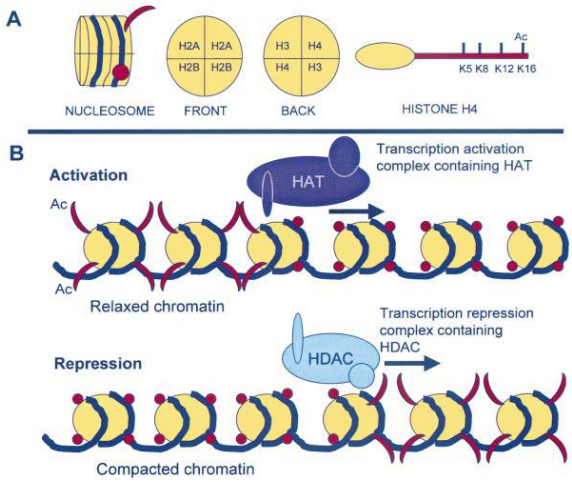

Figure 1. Illustrates several different aspects of transcription and the role of histone modification in this process. This diagram represents two schematic data, the first part A represent the composition of histone and the second part B shows both of expression and repression of the transcriptional process which take place in chromatin. This diagram was taken from [16].

It has been proposed that the histone modifications affect indirectly on the chromatin structure by permitting other specific proteins to modified histones [17]. Several medical studies have proven that the transcriptional process is commonly accompanied by an alteration of histone acetylation [15]. The process of histone acetylation is controlled by two antagonise enzyme activities which known as Histone acetyltransferases (HATs) and Histone deacetylases (HDACs) .The latter will discuss in this section in much more detail. Many of the HATs can be grouped into at least five families upon the structural motifs and their ability

to acetylating histone, there is difference in the functional performance domain attributed to affinities of some HATs to specific cellular targets, the table below was accumulated from Wynne Aherne, Rowlands [18]. The table below demonstrates the classification of HATs [18].

Classifications of HATs

Table 1. Illustrates the Summary of the most common types of histone acetylasetransferases (HATs) families.

Family	Member	Size (kDa)	Complex/interacting proteins	Target
GCN5/PCAF	GCN5 PCAF Elp3	95 90 60	STAGA, TFTC PCAF complex Elongator for RNA polymerase II	H3/H4, nonhistone proteins
p300/CBP	p300	300	unknown	H3, H4, H2A, H2B, nonhistone proteins
TAFII250 Nuclear receptor coactivators	CBP TAFII250 ACTR SRC/TIF2	260 250 150	TFIID Unknown	H3/H4,nonhistone Proteins H3/H4
MYST (MOZ, YBF2/SAS3, SAS2, Tip60)	ESa1 Tip60 MOF MOZ	- 60 - 225	NuA4 Tip60 complex MSL complex MSL complex	H3, H4, H2A

Recently, a great deal of research interest has been found that histone acetyltransferases cannot combined directly to DNA, they are attached to promoters the tools of DNA bound transcription factors.

Histone deacetylases

To date, 18 mammalian histone deacetylase enzymes have been identified. HDAC is classified into three main classes; the class 1, class 2, class 3. " [16]. Moreover, recently it has been discovered another subclass which shares similar features to class 1 and class 2 ".In addition it has yet to be assigned to a specific class" [19]. Despite the fact that both HATs and HDACs have contradictory actions, they share most common characteristics features. For example, HDACs are able to bind to other proteins which take part in the regulation of gene expression [20]. This table was taken from Hess-Stumpp [19].

On one hand, it is well-known that process of acetylation ; it is the process of addition of an acetyl group which is mediated by HATs in turn due to diminishing the positive charge of histone mainly H3-H4 [21]. When the level of HATs is increased the transcription process is augmented [22]. Furthermore, acetylation of histone leads to relaxing the chromatin enabling DNA-nucleosome interaction to have more accessible to transcription factors [23]. The levels of histone acetylation have a major role in chromatin remodeling and in the regulation of gene transcription" [24]. On the other hand, HDAC enzymes responsible for deacetylation of lysine residues; withdrawal of an acetyl group by charge relay system, thereby decreasing the accessibility of transcription via decreasing the space between the nucleosome and DNA which yields a more compact chromatin resulting a transcriptional repression [16]. Collectively, these findings show that any defect occurs in the gene expression and repression is controlled by HATs and HDACs is the strategy applied by oncogenes. Moreover, any inappropriate changes in the structure of chromatin leads to neoplasm cell transformation. It is clear that, several researchers used the principle of histone modification in further trials and by using this concept of targeting the carcinoma cells and blocking their development aiming to find appropriate and effective therapy against most fatal malignancies. In comparisons to previous treatments which were limited in their therapeutic indicators. Moreover, these kinds of drugs caused several biological functional changes either on transformed cells or normal cells without distinguishes [8]. Clearly, a good understanding

of this background concept is extremely important to the progression and development of efficient HDAC inhibitors used in treatments of particular malignancies.

Table 2 Classification of HDACs and their features.

Class of HDAC	HDACS identified	properties
Class I	HDAC 1, 2, 3, 8	Homologous to yeast RPD3 protein; detected almost exclusively in nucleus; ubiquitous expression in various human cell lines and tissue
Class II	HDAC 4, 5, 6, 7, 9, 10	Homologous to yeast HDA1 protein; less restricted location, shuttling between nucleus and cytoplasm in response to certain cellular signals; may be involved in cellular differentiation and development
Class III	SIRT 1, 2, 3, 4, 5, 6, 7	Homologous to yeast SIR2 protein; require NAD+ for gene regulatory activity
Other	HDAC 11	Recently discovered; shares features of Class I and Class II HDACs and has yet o be assigned to a specific class

Classification of HDAC inhibitors

There are six classes of histone deaceytlase inhibitors (HDACi) which are classified upon their structure; 1.Hydrodroxamic acid derived compound such as Trichostatin A (TSA), Suberoylanide hydroxamic acid (SAHA).2.Cyclic tetrapeptides for instance, Depsipeptide (FK228) and Trapoxin.3.Short chain fatty acids which include Valproic acid , Phenyl butyrate.4.Synthetic benzamide such as Tacedinaline.6.Ketones include Trifluoromethyl ketone [19]. The table 3 below shows different types of HDACs inhibitors with examples. This table adapted from Hess-Stumpp [19]. These inhibitors have the capability of stimulation the erythroleukemic cells to differentiate.

Table 3 Natural and manufactured HDACs inhibitors.

Group	Examples
Hydroxamic acid derived compounds	Trichostatin A(TSA)
	Suberoylanilide hydroxamic acid(SAHA)
	M-carboxycinnamicacid-bishydroxamide(CBHA)
	Azelaic bis-hydroxamic acid(ABHA)
	NVP-LAQ824
	LBH589
	Oxamflatin
	PXD101
	Scriptaid
Hydroxamic acid derived compounds	Pyroxamide
Cyclic tetrapeptides	Depsipeptide (FK228; FR901228)
	Apicidine
	Trapoxin
	HC-toxin
	Chlamydocin
Short –chain fatty acids	Depudesin and CHAPS

	Valproic acid (VA) Phenyl butyrate (PB) Phenyl acetate (PA) Sodium butyrate (SB) AN-9 (Pivanexs)
Synthetic pyridal carbamate derivative	MS-275
Synthetic benzamide derivatives	CI-994(*N*-acetyaldinaline) (Tacedinaline)
Ketones	Trifluoromethyl ketone Alpha-ketomides

Histone deacetylase mechanisms

It is known that cancer causes alteration in major cellular processes such as cell cycle, programmed cell death (apoptosis), cell adhesion and angiogenesis [25]. Several classes of histone deaceytlase inhibitors have shown a potent role to treat many of haematological malignancies by elevate the induction rate of apoptosis in several cells [26]. HDAC inhibitors strongly promote programmed cell death (Apoptosis) in the cancer cells at G1/S stage, which leads to induce the expression of one the most common genes the cyclin –dependant inhibitors P21 thus due to P53 induction [27]. Furthermore, HDAC inhibitors have vital and effective role in the angiogenesis; is the process of formation of new blood vessels from preexisting blood vessels which allows tumours to grow and metastasis. HDACi exhibits antiangiogensis activity [28]. Landmark studies have suggested that HDAC inhibitors exert their potential action via major pathways such as apoptosis and their ability to stimulating reactive oxygen species [27]. This is brief information about HDAC inhibitors mechanisms. Firstly, programmed cell death includes two pathways, extrinsic pathway (death receptor pathway) and intrinsic pathway. The former pathway occurs when Tumour necrosis factor related apoptosis -inducing ligand (TRAIL) attach to its receptor such as Death receptor 5(DR5) and FAS ligand (FASL) these due to activation of caspase 8 as consequence leads to apoptosis [25]. Secondly, intrinsic pathway take place when mitochondrial membrane disrupt due to exposure to chemotherapeutic agents as a result all mitochondrial contents spill out and release its contents which include cytochrome c eventually leads to apoptosis [27]. In Carew, Giles [27] paper they demonstrated that HDAC inhibitors have the capability to selectively stimulate apoptosis. However, there is an obstacle to find out the exact and precise key cellular target which is triggered the HDAC inhibitors to inducing response [26].

Some histone deaceytlase inhibitors are very effective especially in lower concentrations. Butyrate is considered as less potent in comparison with the other histone deaceytlase inhibitors .Moreover, butyrate has restriction use to some types of cancer that is attributed to their short serum half life in individual [22]. To date, several clinical studies conducted HDAC inhibitors such as MS-275, Suberoyanilide hydroxamic acid and depsipeptide (FK-228) in haematological trials have shown a preferential clinical impact of these therapeutic agents in haematological malignancies in particular acute myeloid leukaemia and other category of leukaemia [26].

Much has been learned of the physiology of blood from studies throughout vertebrate evolution, it is known that blood cells produced daily in high number and short lived periods. Normal blood consists of three groups of cells; white blood cells (Leucocytes) which protect the body from infection these cells includes , neutrophiles, monocytes , eosinophiles ,basophiles and lymphocytes. Red blood cells (Erythrocytes) contain the haemoglobin which is responsible for carrying the oxygen to tissues and organs, in addition to returning the non oxygenated blood to the lungs. Platelets are necessary for stopping bleeding during exposure to injuries .All these cells derived from one immature blood or marrow stem cells which are known as haematopoietic stem cells that have ability to self-renew and turnover and replenishment throughout the life [29].

Leukaemia means literally cancer of blood cells particularly white blood cells (WBCs) which is characterized by a block in proliferation of WBCs as consequence leads to excessive deposition of malignant leucocytes in the bone marrow and blood [30].

Incidence of leukaemia

Leukemia is a blood cancer marked by the transformation of hematopoietic progenitors and widespread bone marrow infiltration. The primary forms of leukemia include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia

(CLL), and chronic myeloid leukemia (CML)[31]. In 2020, leukemia represented approximately 2.5% of new cancer cases and 3.1% of cancer-related deaths worldwide. The likelihood of developing leukemia varies based on age, gender, and geographical factors, which may be linked to environmental and genetic risk factors' prevalence. Key risk factors for leukaemia include smoking, exposure to certain chemicals, previous chemotherapy, radiation exposure, rare genetic conditions, specific blood disorders, family history, age, and gender [32].

Classification of Leukaemia

There are four types of Leukaemia which are classified according to the degree of the disease and the type of cell .Moreover; there are further subdivision types.1.Acute Lymphocytic Leukaemia (ALL). 2. Acute Myeloid Leukaemia (AML), 3.Chronic Lymphocytic Leukaemia (CLL), 4.Chronic Myeloid Leukaemia (CML) [33]. Acute Leukaemia refers to a disorder which hematopoietic blast cells present more than 20% of a bone marrow cell .Furthermore; the rapid onset considers the characteristic features of this type [33]. It is known that ALL affects about 80%of children. Virtually all childhood malignancies have idiopathic causes, but there are possible environmental causes attributed to leukaemia such as, viruses, radiation, and chemical, also genetic mutations. However, only small numbers of diagnosed cases can be directly related to these causative agents [34]. While the chronic forms show similar properties to the benign tumors of other tissues. It is worth mentioning that both AML and ALL are slightly more common in men than in women [35, 36]. In recent years, there are wide spectrums of drugs used to treat leukaemic patients depend on several factors such as "age, karyotype, mutational status and comorbid conditions" [37]. It has found there is some cases show resistance to cytarabine therefore, specialists tend to replace it with anthracyclines in addition of using other agent to increase the treatment efficiency. Variety of treatment applications have used for patients suffer from leukaemia especially elderly for example, autologous bone marrow transplantation (BMT), allogenic BMT, during the first stages of using these medications shown an improvement. However, the rate of mortality is high [38]. HDAC inhibitors show promising result to various types of malignancies [39].

Novel agents of Histone deacetylase inhibitors:

The first example of HDAC inhibitors is Vorinostat. It is belonging to Suberoylamilide hydroxamic acid (SAHA), is the primitive class of HDAC inhibitor which was acknowledged by the U.S Food and Drug administration (FDA) to treat the skin manifestations of cutaneous T-cell lymphoma (CTCL) [23]. It is traded in the markets under the name Zolinza .It inhibits the activity of these enzymes HDAC1, HDAC2, HDAC3 class I and HDAC6II [40]. Moreover, vorinostat has the ability to interfering with the catalytic sites of histone deaceytlase leads to series of alterations in the cellular proteins via acetylation process which induces cell growth cessation and death of transformed cells [41]

Vorinostat is administrated either intravenously or orally which appears high active either if it is used as a single agent or accompanied by other drugs [23]. However, this observation calls into question .Is vorinostat very effective when it is used in the single application for most of haematological neoplasm transformations?, in recent clinical trials have prove that vorinostat has the disadvantage of not being sufficiently effective in the patients with advance leukaemia stages and other cancer and it is still fully unclear [42]. Figure 2 was accumulated from Richon, Garcia-Vargas [42].

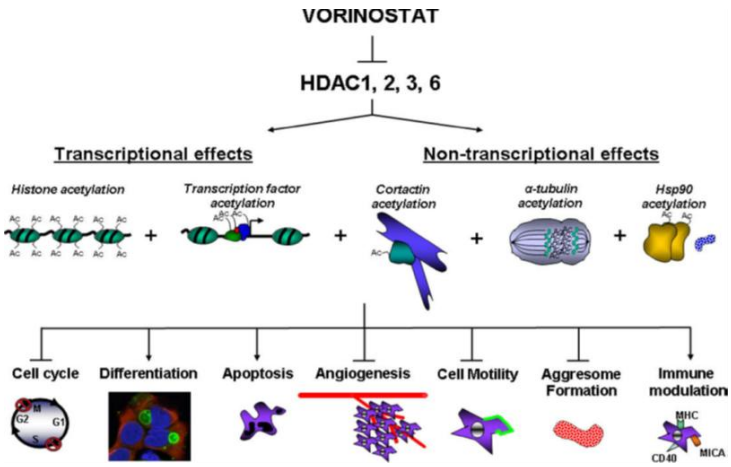

Figure 2: Mechanism of vorinostat on the transformed cells.

This figure demonstrates the effect of vorinostat on the cells either on transcriptional effect or non transcriptional effect.

It has been found that the vorinostat promotes the aceytlation process of histone which leads to increased transcription factors such as p53 in addition to increased several cytoplasmic proteins for example, alpha- tubulin and cortactin also vorinostat promotes the programmed cell death (apoptosis) [42]. Several clinical trials have demonstrated that the oral administration is favourable because of the bioavailability which appears higher in comparison to the intravenous method. Moreover, it has shown that the drug does not interfere with consumption of food and the average half-life of vorinostat oral ingestion is ranged between 91 and 127 minutes higher than the intravenous dose [43]. Many clinical trials and pharmacodynamic studies showed that the bioavailability of vorinostat in both the intravenous and the oral route particularly in Hodgkin lymphoma and cutaneous T cell lymphoma (CTCL) [44]. Moreover, vorinostat plays a crucial role in the diffuse large B cell lymphoma which occurs by an alteration in the regulation of the transcriptional repressor BCL6 [45]. Further studies in lymphoproliferative disorders should address why vorinostat is being effective in Hodgkin lymphoma but not in other types of cancer [46]. However, the promising combination treatment of vorinostat with carboplatin and paclitaxael show preferential efficacy according to Batty report in patients with non small cell lung cancer [23]. However, the major adverse reactions are fatigue, thrombocytopenia (decreased in platelets count) nausea and diarrhoea [40].There are several effective and supportive medications to relieve and prevent these undesired side effects.

Valproic acid

It is a short chain fatty acid which is believed has a limited activity and shows minor responses when it is used as a single therapeutic agents [23]. In the light of this observation most of the clinical studies tend to use valproic acid (VPA) in combination with other DNA methylation inhibitors. Even the clinical studies demonstrate the promising effect and the cure remission but there are increased in the toxic activity with the combinations application especially neuronal activity which calls to performed further random studies in patients with myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) [26]. VPA induces the effect of stem cell factors, thrombopoietin which leads to expansion of the haematopoietic stem cell as a result due to elevation in the rate of self renewal property of the stem cells [26]. This observation of increased the self renewal ability calls into further investigations to avoid the possibility of accelerate leukaemia progression during VPA monotherapy [26].

Trichostatin (TSA).

TSA is a hydromximic compound [47]. Recently, a great deal interest has been found that TSA has the ability to inhibit the growth of the non small cell lung cancer (NSCLC) at lower concentration [48]. TSA induces the programmed cell death and reduces cyclin A expression but increases cyclin E level in addition to, up-regualtion of the target genes of vitamin D receptors, vitamin D plays a major role in antiproliferation as well as its main function to keep both of calcium and phosphorus levels at normal level in the body [48]. Landmark studies have suggested that the combination of drugs currently in use with HDACs inhibitors may be highly effective. For example, the combination between vitamin D and TSA interestingly due to decrease the rate of cell growth particularly in breast and prostatic tumours [49]. These data offer very promising regarding how the combination is effective. However, TSA has the disadvantage of causing excessive cardiotoxicity,therefore a controversy has arisen over the safety of TSA [50]. This data have led to further studies of HDACs inhibitors

which discover other more new effective HDACs inhibitors with high efficiency and low toxicity. It is worth stressing that the combination therapies have been tested and validated in preclinical studies. For example, the combinations between DNA methylation inhibitors and HDACs inhibitors have applied in haematological malignancies such as Decitabine and Azacitidine [51]. Moreover, many studies have shown the efficiency of the combination of vorinostat and 5aza in myelodysplastic syndromes and acute myeloid leukaemia [1, 46]. Table was accumulated from Damia and D'Incalci [46].

Table 5. Different types of histone deacetylase inhibitors are used as therapeutic target.

Drugs	Target	Type of molecule	Clinical development
Cetuximab (Erbitux)	EGFR	MoAb	FDA and EMEA approved (colorectal, head and neck ca)
Panitumumab (Vectibix)	EGFR	MoAb	FDA and EMEA approved (colorectal ca)
Trastuzumab (Herceptin)	HER2	MoAb	FDA and EMEA approved (HER2 overexpressing breast ca)
Erlotinib (Tarceva)	EGFR	SM	FDA and EMEA approved (NSCL, pancreatic)
Gefitinib (Iressa)	EGFR,	SM	FDA and EMEA approved (NSCL)
Lapatinib (Tykerb)	EGFR, HER2	SM	Preregistration for breast cancer in European Union and USA, April 2009
Imatinib (Gleevec)	Bcl-Abl, c-Kit	SM	FDA and EMEA approved (chronic myeloid leukaemia, gastrointestinal stromal tumours)
Dasatinib (Sprycel)	BCR-ABL, SRC family, c-kit,EphA2, PDGFRß	SM	FDA and EMEA approved (Chronic myeloid leukaemia in all phases with resistance or intolerance to imatinib)
Bevacizumab (Avastin)	VEGF-a	MoAb	FDA and EMEA approved (glioblastoma, metastatic HER2 negative breast cancer, NSCL, metastatic colon ca)
Temsirolimus (Torisel)	mTOR	SM	FDA and EMEA approved (renal cell ca)
Sorafenib (Nexavar)	VEGFR, PDGFR, c-kit, Flt3, Raf,	SM	FDA and EMEA approved (hepatocellular carcinoma)
Sunitinib (Suten)	VEGFR, PDGFR, c-kit, Flt3	SM	FDA and EMEA approved (renal cell ca, gastrointestinal ca)
Vorinostat	HDAC inhibitor	Hydroxamic acid	FDA approved (cutaneous T cell lymphoma-third line therapy)

Conclusion

A typically characteristic feature of human cancer is deregulation of cell proliferation and absent of differentiation [52]. Remodeling of chromatin structure in DNA plays a crucial role in the regulation of gene expression which has direct affects on the differentiation and proliferation, particularly post translation modification of the N terminal region of histone core by adding acetyl groups mediated by histone acetyltransferase enzymes HAT. Conversely, deacetylation is a process of removing an acetyl group occurs by histone deacetylase HDAC [53]. Clearly, a good understanding of these two antagonise enzymes are extremely important as a pharmacological treatment of malignant tumours, especially by studying the effect of HDAC inhibitors on the expression of various genes which show their ability to enhance the anticarcinogenic activity compared with other types of chemotherapeutic agents. Hopefully a new breakthrough will occur in this aspect in the future. HDAC inhibitors promote cell cycle arrest in the G1/S stage [54]. Moreover, HDAC inhibitors lead to increase the acetylation process of both H3 and H4 [55] It is noted that by using HDAC inhibitors in most carcinogenic disorders the cure remission rate varies from one patient to another which is not always entirely clear. It is obvious there is still ambiguity about the exact mechanisms of these arsenal weapons against cancer. However, in some leukaemic

cases the principle of HDAC inhibitors in cell cycle arrest and trigger the differentiation of tumour cells is well understood [26]. It is worth mentioning that the combination therapies provide a valuable efficacy which is applied in haematological malignancies such as AML and MDS[1].

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