Review

Histone Deacetylases (HDACs) Guided Novel Therapies for T-cell lymphomas

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Abstract

T-cell lymphomas are a heterogeneous group of cancers with different pathogenesis and poor prognosis. Histone deacetylases (HDACs) are epigenetic modifiers that modulate many key biological processes. In recent years, HDACs have been fully investigated for their roles and potential as drug targets in T-cell lymphomas. In this review, we have deciphered the modes of action of HDACs, HDAC inhibitors as single agents, and HDACs guided combination therapies in T-cell lymphomas. The overview of HDACs on the stage of T-cell lymphomas, and HDACs guided therapies both as single agents and combination regimens endow great opportunities for the cure of T-cell lymphomas.

Key words: Histone deacetylases (HDACs), T-cell lymphomas, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, combination therapy

1. Introduction

1.1 T-cell lymphomas

T-cell lymphomas encompass a heterogeneous group of malignancies comprising 15-20% of systemic lymphomas and less than 10% non-Hodgkin lymphomas. T-cell malignancies are endemic in East Asia, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea. Adult T-cell lymphoma caused by human T-cell leukemia virus-1 is one of the most popular T-cell malignancies. Up to now, there are about 5-20 million patients infected with HTLV-1 around world. According to WHO/EORTC classification based on the clinical pathology indications, T-cell malignancies are divided into extra nodal T cell lymphoma, cutaneous T cell lymphomas (Sézary syndrome and Mycosis fungoides), anaplastic large cell lymphoma, and angioimmunoblastic T cell lymphoma [1]. The clinical performance and pathogenesis are divergent between different T-cell lymphomas; the therapeutic strategies are different but with some overlap especially in their early stage. However, because of the comprehensive pathogenesis and limited therapeutic strategies, patients with T-cell lymphomas usually have a poor prognosis and easy to relapse.

1.2 Current therapeutic strategies for T-cell lymphomas

Currently, chemotherapy is the most preferred treatment in patients with T-cell lymphoma. With the development of intensified chemotherapy, the prognosis of T-cell leukemia/lymphoma has gradually improved. However, due to the non-specific toxicity of current chemotherapeutic compounds to normal cells, the progressive loss of quality of life is a matter of concern [2]. Besides, patients with relapse and resistance to conventional chemotherapy exhibit limited efficacy in the salvage setting.

Recently, the booming targeted therapeutic strategies have become the forefront therapeutics in patients with severe lymphomas and achieved promising therapeutic effects, such as immune therapies of antibodies against CTLA 4 and PD 1 /PDL 1 [3], B cell receptor signaling pathway inhibitors (e.g., ibrutinib [4]), NK cells (e.g., AFM13

[5]), bispecific T engager (BiTE, blinatumomab [6]), T cell receptor (e.g., CART19 [7, 8]). However, all these gorgeous strategies mentioned above have not been testified or not suitable in the treatment of T-cell lymphomas.

The treatment of patients with T-cell lymphomas is challenging. Novel therapeutic strategies are urgently warranted to improve the therapeutic effects of T-cell lymphomas. Thus new flourishing therapeutic targets and techniques (drugs, techniques or combinational trials) would provide opportunities for the treatment of patients with T-cell malignancies. HDACs, kinases, T/B cell receptors, checkpoints or other related key modulators are promising choices. In this review, we will focus on the role of HDACs in T-cell lymphomas and the potential applications as therapeutic targets for the treatment of patients with T-cell malignancies.

2. Histone deacetylases (HDACs)

2.1 Brief profile of HDACs

Histone deacetylases are a class of enzymes deacetylating the acetyl group from ε-N-acetyl lysine amino acid from a histone, which lead to the tight wrapping of DNA. HDACs play a key role in the homeostasis maintenances of histone acetylation euchromatin and heterochromatin in living system [9, 10]. There are 18 HDACs recognized up to now, divided into HDAC I (HDAC 1, 2, and 3: mainly in the nucleus; HDAC 8: partially in the cytoplasm), HDAC II (HDAC 4, 5, 6, 7, 9, and 10: shuttling in and out of the nucleus), as Table 1 showed [11]. Considering the main function of the process of de-acetylation, HDACs act as key epigenetic modulators of essential biological processes by modifying histones of chromatin or non-histone proteins (PTEN, APE1/Ref-1 (APEX1), NF-κB, aggressomes, et al.) [12]. Besides, HDACs are involved in protein degradation, especially HDAC6 that was reported to interfere with HSP90 via degrading HSP90-interacting proteins [13, 14]. HDACs are thought to be the main pathogenic factors to both leukemia and other solid tumors, such as chronic myeloid leukemia, chronic lymphocytic leukemia[15], pediatric acute myeloid leukemia, acute promyelocytic leukemia, renal cancer, colorectal and gastric cancer, breast tumors and so on[16]. In this review, we have focused on the role of HDACs in T-cell lymphomas and the application of HDAC inhibitors as T-cell lymphomas treatments.

2.2 Modes of action in T-cell lymphoma

The elaboration of HDACs in the pathogenesis, therapy and prognosis of T-cell lymphomas would help a lot in the treatment of patients with T-cell lymphomas. The precise mechanisms of HDACs in T-cell malignancies have been investigated under the intervention of HDAC inhibitors (Figure 1), but still not been fully elucidated.

Table 1. Classification of histone deacetylases (HDACs)

Cofactor	Class	HDAC members	Localization
Zn^{2+}-dependent	Class I	HDAC 1,2,3,8	Nucleus (HDAC 8, partially in the cytoplasm)
	Class IIA	HDAC 4,5,7,9	Nucleus/cytoplasm
	Class IIB	HDAC 6,10	Mainly in the cytoplasm
	Class IV	HDAC 11	Nucleus/cytoplasm
NAD^+-dependent	Class III	SIRT 1,6,7	Nucleus
		SIRT 2	Cytoplasm
		SIRT 3,4,5	Mitochondria

2.2.1 Epigenetic modulation

Except for genetic mutation, chromatin differentiation, the reversible epigenetic alterations are the main alterations for cancer initiation, progression and invasion [20]. HDACs interfere with epigenetic chromatin modification by de-acetylating histones and non-histone proteins of nuclear transcription factors mediating carcinogenesis [21]. Besides, HDACs participate in the mediation of oncogenes of *Bcl-xL*-[22], *Bcl2*-[23], or *TCRβ* [22], *c-Myc* [24], *Notch3* [25].

2.2.2 Cytokines regulation

Cytokines are the important participators in immune regulation. A response rate of 30% for cutaneous T-cell lymphoma (CTCL) expressing high affinity IL-2 receptor (IL-2R) was demonstrated in Phases I and II clinical trials of DAB (389) IL-2 by inhibition of histone deacetylases (HDACs) interfering with 0.06 mM arginine butyrate[26]. Up-regulation of HDAC1 and HDAC6 and transcriptional induction of the conco-miR-21 were found in CTCL, which was caused by excessive autocrine secretion of IL-15 in T-cells. IL-15 mediated inflammation was critical in CTCL, and a novel oncogenic regulatory loop between IL-15, HDAC 1/6, and miR-21 was discovered [27]. Besides, HDAC deactivation and concomitant down regulation of CD27 were found in TEL-AML positive leukemia by CD40 ligation [28]. Under the improvement of immune surveillance by CD40 ligation in patients with TEL-AML, a potential increased relapse-free survival was observed with the presence of other risks.

2.2.3 Apoptosis

HDACs mediated the pro-apoptotic response in a decreased way and increased the apoptotic threshold in various hematological and solid
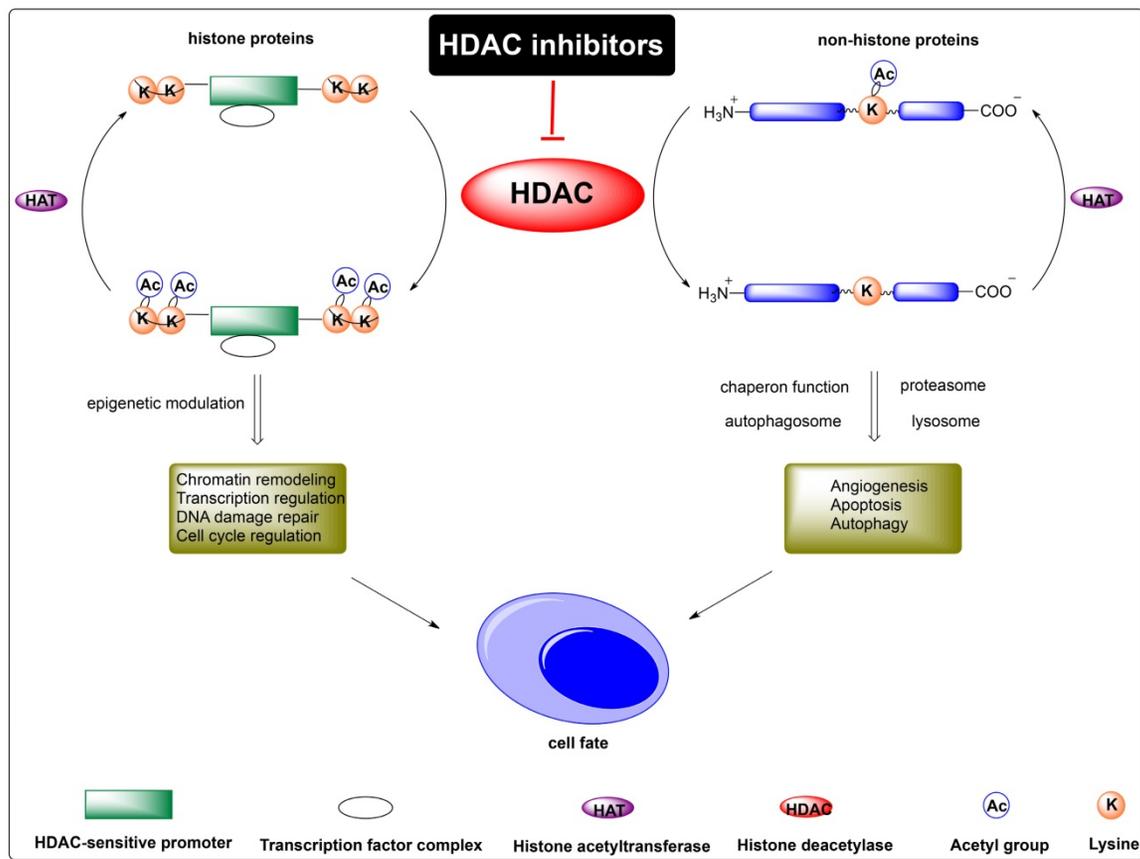
Figure 1. Molecular functions of HDACs. This figure was adapted from Bodiford & Reddy (2014)[17], Hood & Shah (2016)[18], and Weiguo Zhu (2014)[19].

lymphomas. The inhibition of HDAC 1/2 was found to have a synergism effect with BCL11B (a key T-cell development regulator) in the anti-apoptosis effect in CTCL lines [29]. HDACs promoted the acetylation of the chaperone heat shock protein 90 (HSP90), leading to the binding and stabilization of HSP90 client proteins RASGRP1 and CRAF which activate the mitogen-activated protein kinase pathway signaling and down-regulate the pro-apoptotic BCL2 family member BIM both in vitro and in vivo. siRNA of RASGRP1, HSP90 inhibition or HDAC inhibition may contribute to the cytotoxicity and apoptosis induction in lymphoid malignancies by influencing the signal pathway related to HSP90, RASGRP1, CRAF, and BIM [30]. HDAC inhibition by Chidamide induced cell apoptosis by down-regulating Bcl-2 and up-regulating cleaved Caspase-3 and Bax protein expression in peripheral T cell lymphoma [31], MDS cell lines (SKM-1, MUTZ-1) and AML cell line (KG-1) [32]. The induction of tumor suppressor gene RhoB, pronounced expression of p21 and global CpG methylation in the modulation of HDAC were found in CTCL cell lines and tumor cells derived from Sézary syndrome patients by the combined treatment of HDAC inhibitor Romidepsin and demethylating agent Azacitidine [33]. HDAC also has a negative correlation with an anti-apoptotic drug resistance related molecule surviving [34], which was demonstrated by HDAC inhibitor SAHA in the treatment of ATL cells. Considering the important regulation of HDAC in the downstream signal pathway and apoptotic related proteins, HDACs may serve as potential drug target for T-cell malignancies in an apoptosis induction way.

2.2.4 Autophagy

Autophagy is a key self-salvage process to various stresses by degrading long-lived proteins and damaged organelles. Except for the main function on lysine de-acetylation in chromatin, HDACs also have functions in the regulation of plethora of cytosolic proteins with different cellular functions (such as angiogenesis, immune responses, and autophagy) in series of cancers. Treatment of T-cell lymphomas and other cellular studies with effective HDAC inhibitors induced apoptosis, cell-cycle arrest, cell differentiation, anti-angiogenesis and autophagy. In CTCL, HDAC inhibitor SAHA up-regulated the expression of autophagic factor LC3, and inhibited the mammalian target of rapamycin (mTOR) leading to activation of autophagic protein kinase ULK1 [35]. Except for T-cell lymphomas, HDACs were related to

autophagy in other cancers. The novel, potent, selenium-containing HDAC inhibitors (SelSA-1 and SelSA-2) were demonstrated to simultaneously increase in autophagy in lung cancer A549 cells [36]. HDACs have a synergistic effect with autophagy in the process of cellular survival, thus autophagy targeting and HDACs inhibiting offer alternative choice for the treatment of T-cell lymphomas.

HDAC inhibitors usually act at the transcriptional level by interfering with epigenetic chromatin modification and histone de-acetylation [21]. HDAC inhibitors have been shown to induce the acetylation of histone and non-histone proteins (nuclear transcription factors mediating anti-cancer activity), cause DNA damage, promote the re-expression of repressed genes during oncogenesis, mediate lethality through cytokinesis failure, facilitate a pro-apoptotic response and lower the cellular apoptotic threshold in various hematological and solid lymphomas. By modulating these key physiological and pathological processes related to apoptosis, immune response, autophagy and metabolism, HDACs play indispensable role in the pathogenesis and prognosis of T-cell malignancies, which make them prospective target for the treatment of T-cell malignancies.

3. Therapeutic strategies targeting HDACs

3.1 Single agent strategies

The specific functions and structures of HDACs make them ideal drug targets. Various HDAC inhibitors that differ in potency, selectivity, gene regulation, and non-histone protein targets have been investigated. Most HDAC inhibitors have similar mechanism of actions against HDAC by binding to the zinc atom in the catalytic pocket in a non-competitive manner. Nowadays, plenty of HDAC inhibitors have been developed as promising anti-cancer agents; several HDAC inhibitors are now in clinical trials; some have been approved as single anti-tumor agents or adjuvants to traditional chemotherapeutics for many cancers. As for T-cell lymphomas, especially peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), four classes of HDAC inhibitors have been developed. FDA has approved several HDAC inhibitors for the treatment of T-cell lymphomas: Vorinostat (SAHA) for CTCL, Romidepsin for CTCL and PTCL, and Belinostat for PTCL; and Chidamide has been approved by the CFDA for the treatment of relapsed/refractory TCL in China as a single agent. The development of HDAC inhibitors for the treatment of T-cell lymphomas is now flourishing,

many of which exhibit excellent potential in HTLV-1-infected cell lines, ATL cell lines, freshly isolated primary ATL cells, PTCL, and CTCL, such as Romidepsin (cyclic depsipeptide FR901228), Panobinostat (LBH-589), trichostatin A (TSA), and benzamide MS-275. More and more optimization of these reported HDAC inhibitors are now under investigation. In this part, we summarized reported HDAC inhibitors, which have been approved for the treatment of T-cell lymphomas or demonstrated potential efficacy in T-cell lymphomas, as Figure 2 showed.

3.1.1 Vorinostat (suberoylanilide hydroxamic acid: SAHA)

Vorinostat (Zolinza®), also called SAHA, is a hydroxamic acid discovered from screening a series of bishydroxamic acids [37, 38]. Further studies to optimize of the molecular structure and determine the mechanism of action of SAHA showed that by directly binding to the catalytic pocket of HDACs, SAHA inhibited the enzymatic activities of both class I and II HDACs, with an IC50 of less than 86 nM [37, 38]. The cyclic structure of SAHA may be the key point for its specificity. In cellular studies, SAHA effectively inhibited the proliferation of human mantle cell lymphoma cells, human T-cell lymphotropic virus type I (HTLV-1)-infected T cells (MT-1, MT-2, MT-4, and HUT102), established CTCL cell lines, freshly isolated ATL cells and circulating malignant CTCL cells harvested from patients by up-regulating of P21 waf1 protein [39], decreasing the level and phosphorylation of STAT6 protein, and increasing the ratio of NF-κB in the cytoplasm versus the nucleus, leading to growth arrest and apoptosis [40]. Based on its specificity towards HDACs and excellent performance in T-cell lymphomas, SAHA was tested in a multicenter clinical trial in patients with refractory and relapsed CTCL, and showed excellent therapeutic potential, with an ORR of 24% [41] (30% [42]) and duration of response of approximately 4 months [41] (longer than 6 months [42]) in two single-arm phase II studies. In an extension study, 32% of overall patients experienced improving pruritus relief and high quality of life. Based on these promising therapeutic effects, Vorinostat was first approved as an HDAC inhibitor in 2006 for the treatment of relapsed/refractory cutaneous T-cell lymphoma (CTCL) patients with recurrent disease on or after 2 systemic therapies as an oral agent named Vorinostat in USA [43] and Japan and achieved orphan drug designation in Europe. Vorinostat is now the only approved drug for the treatment of relapsed/refractory CTCL with a daily recommended dose of 400 mg [44]. According to
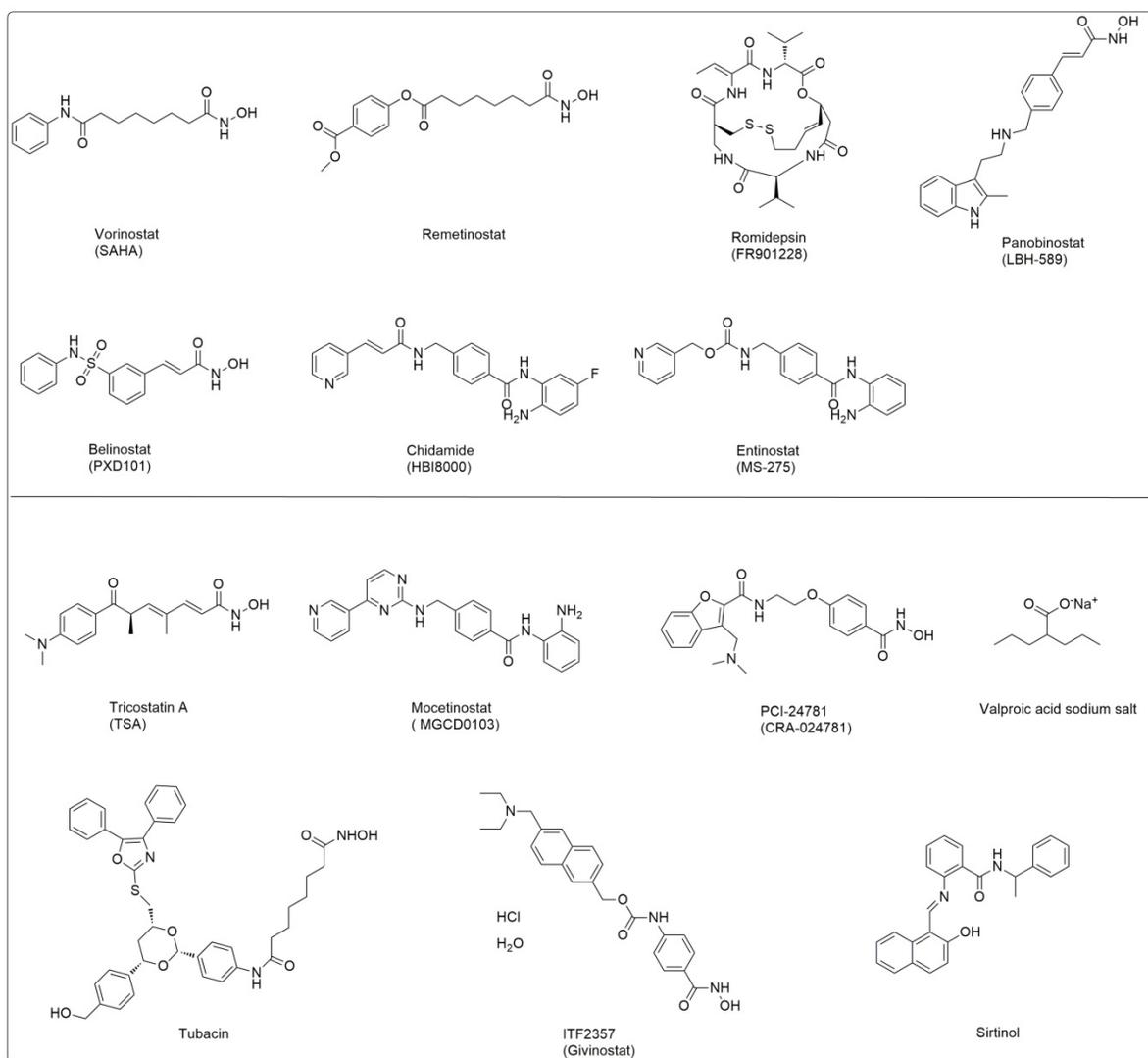
Figure 2. Chemical structures of HDAC inhibitors.

reports, glucuronidation by the uridine diphosphate glucuronosyl-transferase (UGT) enzyme system was identified as the key process mediating the metabolism and excretion of Vorinostat, while the cytochrome P-450 isoenzyme system was not found to participate in the metabolism of Vorinostat [45]. UGT1A1 might play an important role in Vorinostat toxicity and response levels in related patients. Until now, warfarin and valproic acid have demonstrated obvious drug interactions with Vorinostat, which should be noticed in the clinic [46]. Vorinostat shows a favorable safety profile and well tolerance at the approved once-daily dose of 400 mg. The most common adverse events of Vorinostat are of grade 1 or 2 (such as fatigue, nausea, and diarrhea), while more severe toxicities (such as thrombocytopenia, fatigue, and nausea) only occur in less than 6% of patients [47, 48]. Except for R/R CTCL, Vorinostat has exhibited promising therapeutic effects and

manageable safety profiles [49] against other hematologic lymphomas (such as multiple myeloma (MM) [50], indolent NHL[51, 52], relapsed/refractory acute myeloid leukemia (AML) [53, 54], myelodysplastic syndrome (MDS)) [50, 54, 55], glioblastoma multiforme [56, 57], advanced leukemias [50], and solid tumors [58] as a monotherapy or as a combination therapy with other agents (e.g., PIs and IMiDs) at doses tolerated by patients. The optimization of the structure of Vorinostat and studies on its efficacy in other lymphomas are now under investigation.

3.1.2 Romidepsin (cyclic depsipeptide FR901228)

Romidepsin (also called FR901228) is a natural product isolated from the bacterium *Chromobacterium violaceum*; this product has a typical cyclic depsipeptide structure, and primarily displays an inhibitory effect on class I HDACs and a weak effect on class IIB (HDAC 6) [59, 60]. This inhibition was

found to have potent effects on T-cell lymphomas. Romidepsin acts as a prodrug, and its mode of action was elucidated in 1998 [61]. The key interaction of Romidepsin with HDAC is it's binding to the zinc atom in the binding pocket of Zn-dependent histone deacetylase after reducing the disulfide in cells [62]. Romidepsin has shown excellent anti-cancer effects by interfering with the cell cycle, cell motility and angiogenesis, thus inducing cell death and differentiation. Romidepsin exhibited effective durable responses in patients with relapsed/refractory CTCL as a single-agent therapy. The FDA approved Romidepsin in 2009 for the treatment of cutaneous T-cell lymphoma (CTCL) patients who have received at least 1 prior systemic therapy [63, 64]. Besides, it has shown excellent inhibitory effects on malignant lymphoid cell lines, including HTLV-1-infected T-cell lines, primary adult T-cell leukemia and peripheral T-cell lymphoma (PTCL) cells by blocking the Notch 1 pathway [65] and the NF-κB pathway [66]. Romidepsin has demonstrated durable clinical responses in patients with relapsed/refractory PTCL [64, 67-72], leading to its approval by the FDA in June 2011 for the treatment of PTCL in patients who have received at least one prior therapy. Combination therapies of Romidepsin with other agents are now in clinical trials, for example, Romidepsin plus CHOP is in a phase Ib/II trial of patients with newly diagnosed PTCL (NCT01280526, NCT01796002) [73], and a combination therapy using Romidepsin and pralatrexate has shown synergy in preclinical studies[74]. All these ongoing trials have shown the potential of Romidepsin in the treatment of PTCL. In conclusion, Romidepsin exhibits outstanding effects on the treatment of CTCL and PTCL as a single agent and has potential as a single agent or in combination with other effective agents for the treatment of T-cell lymphomas. It would be worthwhile to further explore the application and optimization of the chemical structure of Romidepsin to improve its efficiency and safety/tolerability.

3.1.3 Belinostat (PXD101)

Belinostat (PXD101), N-hydroxy-3-[3-(phenysul-famoyl) phenyl] prop-2-enamide, is a low-molecular-weight pan-HDAC inhibitor with a sulfonamide-hydroxamide structure developed by TopoTarget [75]. Belinostat exhibits nanomolar potency towards class I, II and IV HDAC isoforms by chelating hydroxamate with zinc ions essential for the enzymatic activity of HDAC. Belinostat has demonstrated meaningful efficacy and a favorable toxicity profile towards serious hematological lymphomas and solid tumors [76, 77]. The

encouraging efficacy of Belinostat in T-cell lymphoma has accelerated its development as a therapeutic agent [17, 18]. In clinical trial of patients with relapsed/refractory PTCL [78, 79], Belinostat exhibited promising efficacy and a highly favorable safety profile (minimal grade 3 and grade 4 toxicity) [80]. In addition, this inhibitor is especially well tolerated in patients with thrombocytopenia and shows promising benefits. Based on these conclusive therapeutic effects, Belinostat (BELEODAQ™, Spectrum Pharmaceuticals, Inc.) has been accelerated approved by the FDA in July 2014 as an orphan drug and fast track designed for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) by intravenous administration[81, 82]. The safety and efficacy of Belinostat has made it a first-line drug for R/R PTCL, and combination treatments using Belinostat with other front-line therapies are now in clinical trials, which will be further elucidated in the section on combination therapies in this review. Other than the use of Belinostat in the treatment of PTCL, the clinical application of Belinostat in solid tumor lymphomas [76, 79, 83-85], refractory acute leukemia [84, 86, 87], myelodysplastic syndrome [88], and nonsmall-cell lung cancer [89, 90] has also been further evaluated. In any case, these results guarantee the expansion of applying Belinostat in cancer therapy and offer more therapeutic choices for PTCL. This novel HDAC inhibitor may thus represent a breakthrough in the treatment of T-cell lymphomas and other HDAC-related solid cancers.

3.1.4 Chidamide (HBI-8000)

Chidamide (HBI-8000 or CS055) is a synthetic analog of MS-275 screened from various benzamide-prototype compounds and further rationally designed by molecular docking employing an HDAC-like protein, which was independently developed by Chipscreen Biosciences in China as an innovative new drug. In the following chemical genomic-based analyses and other molecular biological evaluations, Chidamide exhibited subtype-selectivity towards class I HDACs (HDAC 1, 2, 3) and class IIb HDAC (HDAC 10) by targeting the catalytic pocket [91]. Cellular assays showed the efficient anti-cancer activity of Chidamide in ATL-derived cell lines, primary ATL cells, myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) cell lines in a time- and dose-dependent manner by increasing histone H3 acetylation at Lys9/Lys18 and H4 at Lys8 [91], immune cell (NK cells and CD8 cells)-mediated cytotoxicity [91], epigenetic modulation [31], cell cycle arrest at G0/G1 phase [31, 32, 92], apoptosis by

JAK2/STAT3 [93] and Bim and NLR family pyrin domain containing 3 (NLRP3) inflammasome pathway activation [94]. Based on its efficiency in ATL cells, Chidamide was further developed as an anti-tumor agent in PTL patients, especially in treatment-naive or relapsed patients. In addition, its efficacy and safety have been further demonstrated in non-Hodgkin's lymphoma in phase I and II clinical trials, with an overall response rate (ORR) of 39.06, disease control rate (DCR) of 64.45% and median progression-free survival (PFS) of 129 (95% CI 82 to 194) days as a single agent [51, 95, 96]. After oral administration in patients, Chidamide showed excellent potential in overcoming drug resistance, tumor cell metastasis, and recurrence by inducing tumor stem cell differentiation, drug-resistant tumor cell reversal, and epithelial-to-mesenchymal transition [31]. The adverse events (AEs) of Chidamide were mostly grade 1/2, while more than 5% patients showed grade 3 or even higher adverse events (such as thrombocytopenia in 10.2% of patients and neutropenia in 6.2% of patients) after receiving Chidamide monotherapy [96]. Encouraging preliminary anti-tumor activity, favorable PK and PD profiles, and safety profiles of Chidamide were demonstrated in serial clinical trials, especially in patients with T-cell lymphomas [31]. The China Food and Drug Administration (CFDA) as an oral agent for the treatment of relapsed or refractory PTCL approved Chidamide in December 2014. Long-term survival potential was observed in PTCL patients after treated with Chidamide. Moreover, clinical trials are currently ongoing in the United States (Clinical Trials Identifier: NCT02733380) and Japan for ATL/PTCL patients. In addition to ATL/PTCL, Chidamide also exhibited a broad-spectrum of therapeutic effects against other hematological lymphomas [92] and solid cancers (such as lung [97, 98], colon [99, 100], liver [101] and pancreatic [102-104] carcinoma) as shown in athymic nude mice subcutaneously inoculated with different human tumor cell lines. Further investigation of its potential efficacy, safety profile and mechanism as a single agent or combination therapy in T-cell lymphomas and solid tumors is now underway.

3.1.5 Panobinostat (LBH-589)

Panobinostat (LBH589) is a novel cinnamic hydroxamic acid derivative with excellent inhibitory activity against class I (HDAC 1, 2, 3, and 8), II (HDAC 4, 5, 6, 7, 9, 10), and IV (HDAC 11) HDAC enzymes, and is defined as a pan-deacetylase inhibitor [105]. As a pan-DAC inhibitor, Panobinostat exhibited at least 10-fold more potency than other HDAC inhibitors (such as Vorinostat) and appears to

be the most potent pan-DAC inhibitor. In vitro, Panobinostat has shown potent cytotoxicity at nanomolar LD90 (90% cell death, 14-541 nM) in many hematological lymphomas, such as multiple myeloma [106-109], WM cells and cell lines [110], acute myelogenous leukemia [111], and cutaneous T-cell lymphoma [112-115]. Panobinostat was approved in February 2015 for the treatment of relapsed/refractory MM patients who had gone through at least two prior regimens, including Bortezomib and an immunomodulatory agent in combination with Bortezomib and Dexamethasone by the US FDA and the European Medical Association (EMA). Studies of the anti-tumor effects of Panobinostat in T-cell lymphoma, such as cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma cells, are ongoing. The anti-tumor potential of Panobinostat has been attributed to the inhibition of angiogenesis and migration [116], disruption of endothelial cell chemotaxis, and induction of apoptosis [117] and autophagy [118]. Panobinostat was shown to induce hyperacetylation of core histone proteins of the chromatin such as histone H3 and H4, deregulation of Polycomb repressive complex 2 (PRC2) by over-expressing Enhancer of zeste homolog 2 (EZH2) [119, 120], SUZ12 [119], EED and CCR6, downregulation of miR-150 and miR-185-5p in advanced CTCL [112], modulation of epigenetic genes, reactivation of epigenetically silenced tumor suppressor genes (such as *p21* and *TP53* [121]), and regutation of signaling pathways (Akt [122], Sirt1 [114], NF-κB, Bcl-2 and STAT3/STAT5 [114]). The clinical efficacy of Panobinostat by oral and IV administration has been demonstrated in advanced cutaneous T-cell lymphoma (CTCL) [113]. In a phase I dose-escalation study of oral Panobinostat, two patients achieved CR and four achieved PR among ten CTCL responding patients, while dose-limiting diarrhea and thrombocytopenia were observed [115]. Panobinostat exhibited acceptable tolerability and modest overall clinical responses in CTCL patients with a manageable safety profile. Microarray analyses showed that a unique set of genes related to apoptosis, immune regulation, and angiogenesis were altered after Panobinostat treatment [115]. A phase II trial of oral Panobinostat in patients with refractory cutaneous T-cell lymphoma (CTCL) failed at least two systemic therapies with relatively low response rates and short time to progression (CRs: 15 of 95 patients) [123]. In a phase II trial of oral Panobinostat in a total number of 139 patients with MF/SS refractory to 2 standard therapies, the median TTRs was 2.3 months in bexarotene-exposed group (n=79), while 2.8 months in bexarotene-naïve group (n=60); the median DORs of bexarotent –exposed group was 5.6 months;

the median PFS rates of bexarotent –exposed group was 4.2 months and 3.7 months for bexarotene-naïve group [113]. Patients with PTCL-NOS and CD4+ hematodermic T-cell lymphoma exhibited potential responses after being treated with Panobinostat (NCT00901147) [124]. The most common adverse effects of Panobinostat were diarrhea, nausea, fatigue, pruritus, thrombocytopenia, and decreased appetite. The potential study of Panobinostat in advanced or refractory CTCL have been promoted into phase II clinical trials as a single agent or combination treatment. Besides, Panobinostat is currently being evaluated in an ongoing clinical study for peripheral T-cell lymphoma [125]. Although Panobinostat exhibited excellent anti-tumor potential in T-cell lymphoma patients with acceptable tolerance and a manageable safety profile as an oral agent, based on the completed clinical trials, any government institute has not yet approved it. Further investigations and more clinical trials of Panobinostat in T-cell lymphomas as a single agent or in combination with other anti-tumor agents are in full swing. In any case, the properties of Panobinostat in T-cell lymphomas (anti-tumor potency, safety profile, tolerance, oral formulation, long half-life, etc.) have made it an attractive alternative therapeutic agent for T-cell lymphomas, especially cutaneous T-cell lymphoma and adult T-cell leukemia/lymphoma.

3.1.6 Remetinostat

Remetinostat is a class of benzoic acid targeting HDACs, which was developed by Medivir AB for the treatment of early-stage cutaneous T-cell lymphoma (CTCL). Unlike other systemic HDAC inhibitors, remetinostat was designed to be active within cutaneous lesions and to be quickly decomposited in the bloodstream, preventing exposure to the whole body. Based on this specificity, remetinostat exhibits high efficacy in the skin with mild side effects. Medivir AB has recently announced that remetinostat, the topical skin-directed histone deacetylase (HDAC), has completed a 60-subject phase II clinical study in patients with an early-stage mycosis fungoides (MF) variant of CTCL in which remetinostat showed good tolerance without signs of systemic adverse effects in all dose groups. The full phase II trial data will be presented at scientific meeting in the second half of 2017. Based on the efficacy and safety data from this phase II study, Medivir expects to carry out a phase III study later this year after discussing the data and protocol with regulatory authorities. The promising therapeutic benefits and safety make remetinostat a promising therapeutic treatment of patients with CTCL, a chronic and poorly treated orphan disease.

3.1.7 Entinostat (MS-275)

Entinostat (SNDX-275 or MS-275) is a synthetic benzamide derivative showing activity against HDAC 1 (IC50=0.51 μM) and HDAC 3 (IC50=1.7 μM) and anti-tumor activity in solid cancers (bladder cancer, metastatic kidney cancer, non-small cell lung cancer, and myeloid lymphomas) and lymphomas (e.g., B-cell chronic lymphocytic leukemia [126]). Entinostat has been tested in many clinical trials in patients with advanced and refractory solid tumors or lymphoma [127-130] as a single agent or in combination with other agents, such as in metastatic kidney cancer (Clinical Trials Identifier: NCT01038778), relapsed and refractory myeloid lymphomas (phase II study, Clinical Trials Identifier: NCT00466115), non-small cell lung cancer (Clinical Trials Identifier: NCT00387465) [131-133]. Entinostat has been demonstrated to effectively inhibit the proliferation of both human T-cell lymphotropic virus type I (HTLV-1)-infected T cells (MT-1, MT -2, MT -4, and HUT102) and freshly isolated ATL cells harvested from patients by interfering NF-κB signaling and inducing apoptosis [39]. Although entinostat has exhibited exciting anti-tumor potency, its toxic effect cannot be ignored. Thus, in order to benefit from its potency as an anti-tumor agent, more efforts should be made in order to improve its toxicity via optimization of its chemical structure.

In addition to the HDAC inhibitors mentioned above that have been studied intensively, many other exciting HDAC inhibitors have been developed, such as PCI-24781 (abexinostat), ITF- 2357 (givinostat), MGCD 0103 (mocetinostat), FK228 (Romidepsin), and valproic acid [134]. These HDAC inhibitors have exhibited promising potency towards HDAC enzymes and therapeutic effects as single agents or adjuvants to existing therapeutic strategies.

3.2 Combinational therapies

On the way to the discovery of ant-cancer therapies, combination therapies have occupied considerable markets in clinical. Combination therapies take advantages of many effective therapies (such as chemotherapies, targeting therapies, and immune therapies) and synergistic effects were demonstrated in patients with malignancies. Upon regulating related histone and non-histone proteins, HDACs participated in serious cellular processes, proliferation, epigenetic modulation, cytokine secretion, apoptosis, autophagy, signal transduction network, immune modulation, and so on. We have introduced the effective HDAC inhibitors as single agents for the treatment of T-cell lymphomas aforementioned. Considering the participation of HDACs in complex cellular processes, the

combination therapies of HDACs inhibition and others against T-cell lymphomas are worth to explore and verify elaborately. The combination of HDAC inhibitors and other anticancer agents may exhibit synergistic efficacy in the treatment of T-cell lymphomas. However, reviews on HDAC-guided combination therapies for T-cell lymphomas are sparse. In this section, we have gone through the potential HDAC-guided combination therapies in the treatment of T-cell lymphomas both preclinical and clinical. Data regarding combination treatments with HDACIs is sparse.

Table 2. Current statuses of HDAC inhibitors applied in T-cell lymphomas.

Name	Chemical structure	Activity		Disease	Adverse effects	Status	Administration	Ref
		Enzyme	IC50/nM					
Vorinostat	 CAS:149647-78-9	Class I Class II	< 86	R/R CTCL	Common side effects	US FDA Japan Europe	Oral	[37-44]
Romidepsin	 CAS:128517-07-7	HDAC 1 HDAC 2	36 47	CTCL R/R PTCL	Acceptable	US FDA	Intravenous	[59-74]
Belinostat	 CAS: 866323-14-0	Class I Class II Class IV	Nano molar potency	R/R PTCL	Acceptable	US FDA	Intravenous	[17, 135, 136]
Chidamide	 CAS: 743420-02-2	Class I : 1,2,3 Class II b: 10		R/R PTCL ATL PTCL	Grade 1 to 2	CFDA Clinical trial US Japan	Oral	[31, 32, 51, 91-96]
Panobinostat	 CAS: 404950-80-7	Class I Class II Class IV	Pan-HDACi	ATL CTCL PTCL	Common side effects	Phase II	Oral	[105, 107-121, 123, 124, 137]
Remetinostat	 CAS: 946150-57-8			CTCL	No systemic AE	Phase II		Medivir AB
Entinostat	 CAS: 209783-80-2	HDAC1 HDAC3	510 1700	ATL	Toxic	Preclinical		[39]
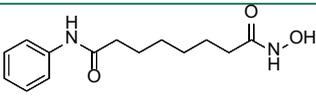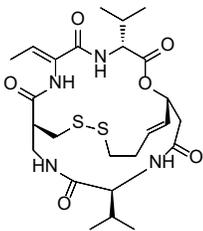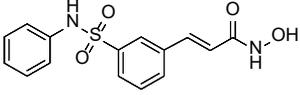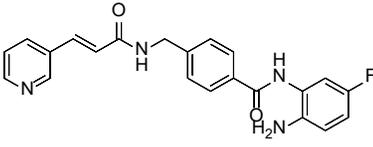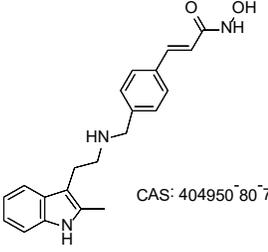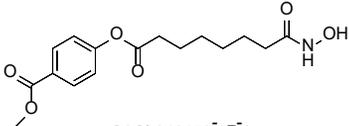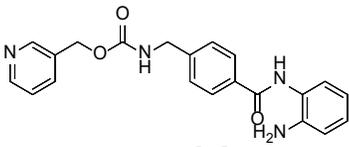
3.2.1 Belinostat based combinational therapies

Belinostat (PXD101) is a pan-HDAC inhibitor with a sulfonamide-hydroxamide structure developed by TopoTarget[138]. Belinostat has become a first-line drug for R/R PTCL based on its high efficacy and acceptable safety profile. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like strategies are recommended as the first-line treatment for PTCL, but the prognosis remains poor with a high possibility of relapsing within 5 years. Belinostat and components of the CHOP strategy have different cellular targets and mechanisms of action, there will be a great chance that Belinostat and CHOP- or CHOP- like strategy has a synergistic effect against patients with PTCL. A phase I study of 23 patients with PTCL was carried out for the investigation of effect of Belinostat and CHOP (NCT01839097)[139]. In this study, a response rate of 89% (16 of 18 evaluable patients) was demonstrated upon the treatment of Belinostat (standard therapeutic doses) and CHOP, and the adverse events were those typically reported with CHOP alone, such as neutrophil count decreased (26%), anemia (22%), neutropenia (17%) and white blood cell count decreased (17%). A study of Belinostat and Bortezomib in treating patients with relapsed or refractory acute leukemia or myelodysplastic syndrome has been completed (NCT01075425). A study of Belinostat plus Carfilzomib in relapsed/refractory NHL (non-Hodgkin lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, peripheral T-cell lymphoma) is currently recruiting participants (NCT02142530). A study of volasertiv and Belinostat in patients with relapsed and refractory aggressive B-cell and T-cell lymphomas is waiting for the participant recruitment (NCT02875002). Another study of Belinostat therapy with Zidovudine for adult T-cell leukemia-lymphoma is currently recruiting participants (NCT02737046).

Table 3. Belinostat based combination therapies.

Agent1	Agent2	T-cell lymphomas	Progress	Clinical trial	Ref.
Belinostat	CHOP	R/R PTCL	Phase I	NCT01839097	[132]
	Carfilzomib	R/R NHL (including PTCL)	Phase I	NCT02142530	
	Bortezomib	Acute leukemia or myelodysplastic syndrome	Phase I	NCT01075425	
	Volasertiv	R/R T/B-cell lymphomas	Phase I	NCT02875002	
	Zidovudine	Adult T-cell leukemia-lymphoma	Phase I	NCT02737046	

All these clinical trials of Belinostat (Table 3) with other agents ongoing or completed for the treatment of patients with T/B cell lymphomas or other hematological malignancies or other solid tumors exhibited the potential therapeutic effect of Belinostat in these malignanices, providing alternative options for patients with malignancies and opportunities for doctors and drug researchers.

3.2.2 Vorinostat (SAHA) based combination therapies

Preclinical experiments of Vorinostat with the inhibition of methyltransferase or proteasome, or with DNA-damaging agents (radiation or chemicals induced) have demonstrated promising synergistic activity in specific tumor types. After treating with Vorinostat, the cellular DNA methyltransferase was up regulated, which could be preclinically abrogated by DNA methyltransferase inhibition. This synergistic effect could increase the lethality of tumor cells, offering new opportunity for combination therapy in tumors. A clinical study of 60 patients with refractory or poor-risk relapsed lymphoma (26 with diffuse large B-cell lymphoma (DLBCL), 21 with Hodgkin lymphoma, 8 with T-cell lymphoma, and 5 with other B-cell lymphomas) was conducted to test the clinical combination effect of Azacitidine with Vorinostat/Gem/Bu/Mel (NCI201102891) [140]. In the follow-up of 15 months, patients with T-cell lymphoma have 88% of event-free and overall survival rates observed after treating with the combination therapy. The event-free and overall survival rates are very promising in other patients with lymphomas (65% and 77% among patients with DLBCL, 76% and 95% among patients with Hodgkin lymphoma). In another clinical study of 78 patients (52 DLCL, 20 HL, and 6 T-lymphoma) between ages 12 to 65, 5 of 6 patients with T-NHL were alive in CR at 16 to 29 months after treating with the combination therapy at the median follow-up 25 months [141]. The main toxicities included mucositis, dermatitis, neutrophils and platelets, with no treatment-related deaths. This clinical trial of Vorinostat and Gemcitabine and Busulfan and Melphalan demonstrated high efficacy and acceptable safety profile in refractory/poor-risk relapsed lymphomas. But further evaluation is still needed when applied widely in clinical. Vorinostat was demonstrated to down regulate nuclear factor kappa beta (NFκβ), leading to the increasing of Rituximab activity. A phase II study was conducting in 28 patients with newly diagnosed or relapsed/refractory indolent NHL to investigate the effect of the combination of Vorinostat and Rituximab [142]. After orally administration of Vorinostat (200 mg twice a day on days 1-14) and Rituximab (375mg/m² on day 1 per 21-day cycle), the ORR of all patients was 46% (67% in the newly diagnosed and 41% in relapsed/refractory patients), and the median PFS was 29.2 months (18.8 months for relapsed/refractory and not reached for untreated patients). A phase I study of Vorinostat

with standard CHOP in patients with newly diagnosed peripheral T-cell lymphoma was also undertaken and good therapeutic effects were gotten [143].

The study of Vorinostat in combination with IFN α and extracorporeal photopheresis in the progressive and/or stable disease of progressive and treatment refractory late stage mycosis fungoides and Sézary syndrome exhibited prolonged efficacy of responses [144]. Vorinostat modifies signaling of T-cell receptor, MAPK, JAK-STAT pathways, and dephosphorylate kinases of ZAP70 (Tyr319, Tyr493) and its downstream target AKT (Ser473). Combination of Vorinostat with PI3K inhibitors or HSP90 inhibitors resulted synergic cytotoxic antagonism in cutaneous T-cell lymphoma cells, which would show potential efficacy for the treatment of T-cell lymphomas [145, 146]. Combination of Vorinostat with the Bcl-2 homology 3 mimetic ABT-737 which blocks Bcl-2, Bcl-XL, and Bcl-w in human T-lymphotropic virus type-I (HTLV-1) infected T-cell lines and fresh ATL cells induced increasing apoptosis and decreasing expression of survivin, offering new choice for the treatment of ATL [23]. The retinoid X receptor (RXR)-agonist bexarotene is a monotherapeutic regimen for cutaneous T-cell lymphomas (CTCLs), and the combination of bexarotene and HDAC inhibitor Vorinostat in vitro leads to synergetic activation of gene transcription and increasing of cell death in human tumor cell lines, but only with low doses of each drug relative to the product label [147]. The proteasome inhibitor Bortezomib also has a synergistic interaction with Vorinostat in cutaneous T cell lymphoma by synergistically inducing apoptosis, providing a rationale for clinical trials of combined proteasome and histone deacetylase inhibition in the treatment of CTCL [148]. Not all the combination therapy of Vorinostat has potential therapeutic effect in T cell lymphomas. In a study of combination of Lenalidomide, Vorinostat and Dexamethasone in 8 patients with relapsed/refractory peripheral T cell lymphoma (PTCL) (2 peripheral T cell lymphoma unspecified, 5 angioimmunoblastic T cell lymphoma, 1 ALK-negative anaplastic large-cell lymphoma) [149]. The median progression-free survival and OS was only 2.2 and 6.7 months separately. The poor therapeutic effects have not terminated the application in T cell lymphomas, but need further investigations with other combination regimens.

HDACs play an important role in the stabilization of DNA double strand. UV$_A$Sens/UV-A phototherapy induced DNA strand breakage by abstraction of H-atoms from 1-deoxyribosyl carbons. In a preclinical study of CTCL Myla cell line, HDAC inhibitors Vorinostat and MS-275 significantly augment UV$_A$Sens/UV-A photochemotherapy-induced cytotoxicity [150]. Further animal models and clinical studies are needed to further evaluate the combinatorial effects of this combination.

3.2.3 Romidepsin related combination therapies

Multiple clinical trials were undertaken in T-cell lymphomas to evaluate the synergestic therapeutic effect of combination therapies with Romidepsin.

Chemotherapy is the first-in line therapy for patients with T-cell lymphomas. The combination of Romidepsin with conventional anti-leukemic agents (Methotrexate, Vincristine, Imatinib, Cytarabine, Carboplatin, Doxorubicin, 4-hydroperoxy-cyclophos-phamide, Etoposide, 6-mercaptopurine and SN-38) has exihibited additive effects in T/B-cell lymphomas, making Romidepsin a promising candidate for the treatment of T/B-cell lymphomas as combination therapies [151]. A phase Ib/II study of Romidepsin and CHOP in patients with newly diagnosed PTCL was evaluated (NCT01280526) [73, 151]. In this study, the combination exhibited excellent therapeutic effect with an ORR of 69%, estimated PFS of 41% and OS of 71% at the median follow-up of 30 months. The most common adverse effects were grade ≥ 3 hematologic and all-grade non-hematologic (such as gastrointestinal, respiratory, or general conditions). A separate phase III study of the comparison of CHOP vs Romidepsin plus CHOP in patients with untreated PTCL is currently recruiting participants (NCT01796002). In the investigation of Romidepsin with ICE (Ifosfamide, Carboplatin and Etoposide), the therapeutic effective was positive with an ORR of 78% (CR: 64%), the median PFS of 10.0 months, OS of 12.5 months, and common grade 3/4 adverse effects of thrombocytopenia and neutropenia (NCT01590732) [152].

Romidepsin has also shown synergistic effects with Lenalidomide in TCL cell lines and relapsed/refractory lymphomas [153], and a few clinical studies have been conducted. In a phase I/II study of relapsed/refractory lymphomas and multiple myeloma (MM), an ORR of 67% in patients with TCL and adverse effects of pneumonia and thrombocytopenia exhibited. In another analysis of 21 TCL patients, the ORR reached 53% (CR: 11%), and the most common AEs were grade ≥ 3 (neutropenia, thrombocytopenia, anemia, and electrolyte abnormalities)[154]. There have been many other clinical trials of Romidepsin and Lenalidomide in the treatment of patients with T-cell lymphomas are undergoing, such as NCT01755975, NCT02341014, NCT02232516, NCT01755975.

Aurora kinase inhibitor alisertib exhibited promising therapeutic effect against TCL as a

single-agent. The combination of Romidepsin and alisertib has shown highly synergistic effect in TCL cell lines through modulation of cytokinesis [155]. A phase I clinical trial of this combination is currently ongoing in relapsed/refractory aggressive B/T-cell lymphomas (NCT01897012) [156]. The therapeutic effect was well in patients with PTCL (1 CR and 1 SD in patients with PTCL up to now), and this therapeutic combination may tend to be more effective in patients with PTCL.

Table 4. Vorinostat based combination therapies.

Agent1	Agent2	T-cell lymphomas	Progress	Clinical trial	Ref.
Vorinostat	5-Aza-2'deoxycytidine	CTCL	Preclinical		
	Gemcitabine/Busulfan/Melphalan	Refractory/poor-risk relapsed lymphomas	Phase I	NCI201102891	[133]
	Rituximab	R/R indolent NHL	Phase II		[135]
	CHOP	Newly diagnosed PTCL	Phase I		[136]
	IFN α and extracorporeal photopheresis	Mycosis fungoides and Sézary syndrome	Preclinical		[137]
	PI3K inhibitors or HSP90 inhibitors	Cutaneous T-cell lymphoma cells	Preclinical		[138, 139]
	ABT-737	Human T-lymphotropic virus type-I (HTLV-1) infected T-cell lines and fresh ATL cells	Preclinical		[17]
	Bexarotene	CTCL	Preclinical		[140]
	Bortezomib	CTCL	Preclinical		[141]
	Lenalidomide/Dexamethasone	R/R PTCL	Phase I		[142]
	UVASens/UV-A photochemotherapy	CTCL Myla cell line	Preclinical		[143]

There is a potential that the combination of Romidepsin and other epigenetic therapies would benefit for the treatment of patients with T-cell lymphomas. The combination of Romidepsin and Azatidine exerted synergistic anti-proliferative effects by inducing apoptosis and changing the global CpG methylation profile in CTCL cell lines and fresh tumor cells isolated from Sézary syndrome patients [33].

In a phase II trial of investigation of the combination of Gemcitabine plus Romidepsin in patients with relapsed/refractory PTCL, the ORR was 30% (CR: 15%), the two-year survival was 50% and progression-free survival was 11.2% [157]. All these patients under investigation were enduring grade ≥3 adverse events (including thrombocytopenia (60%), neutropenia (50%), and anemia (20%)) and mild and transient non-hematological toxicities. The synergy was observed in this trial, but not as prominent as in

preclinical phase. The combination of Romidepsin and pralatrexate exhibited a concentration-dependent synergism against a panel of TCL cell lines in vitro and enhanced efficacy in a NOG murine model of TCL comparing to any single agent, endowing the future clinical application in patients with TCLs [74].

Romidepsin was found to activate the MAPK pathway in HuT78 cutaneous T-cell lymphoma (CTCL) cells, one of the reasons of HDAC inhibitor resistance [158]. Romidepsin also participate in the regulation of chaperone proteins Hsp90, Hsp70 and transcription factors C-MYC and p53. All these comprehensive regulation mechanism make Romidepsin a potential combination regimen. In certain ATL patients, the activity of HDACs, Notch-1 signaling and nuclear factor-κB pathway were increased and constitutive activated. The combination of HDAC inhibitor Romidepsin, γ-secretase inhibitor compound E, and the proteasome inhibitor Bortezomib exhibited significantly enhanced antitumor efficacy in a murine MT-1 model of human ATL, providing rational supports for further clinical trial of this combination therapy strategy in the treatment of patients with ATL [65]. A novel IKK2 inhibitor LY2409881 efficiently suppressed the activity of the NF-κB subunit p65 in lymphoma cells pretreated with Romidepsin, underlying the potential of the combination of Romidepsin and IKK2 inhibitor in the treatment of patients with B/T-cell lymphomas [66]. Romidepsin has also showed synergistic effect with low dose localized electron beam radiation therapy (LEBT) in patients with CTCL, laying foundation for the formal clinical trial of this combination in patients with CTCL [159]. The combination of Romidepsin and interferon gamma may exhibit stabilization of Th1 cytokine profiles and enhanced cytotoxic T-cell activity resulting to a more robust anti-tumor response [160]. A clinical study of the combination of poly ICLC, radiation, and Romidepsin in the treatment of advanced cutaneous T cell lymphoma is currently recruiting participants (NCT02061449).

In addition to the specific treatment of T-cell lymphomas, the combinations of Romidepsin and other therapies have been investigated in other lymphoid malignancies (cutaneous or peripheral T-cell lymphomas included). Many clinical trials for the evaluation of Romidepsin related combination therapy are now recruiting participants, such as Romidepsin plus oral 5-Azacitidine in relapsed/refractory lymphoid malignancies (NCT01998035), Romidepsin and pralatrexate in relapsed/refractory lymphoid malignancies (NCT01947140), Romidepsin, Gemcitabine, Oxaliplatin, and Dexamethasone in

relapsed/refractory aggressive lymphomas (NCT02181218).

Table 5. Romidepsin based combination therapies.

Agent1	Agent2	T-cell lymphomas	Progress	Clinical trial	Ref.
Romidepsin	CHOP	PTCL	Phase III	NCT01280526; NCT01796002	[144]
	ICE (Ifosfamide, Carboplatin and Etoposide)		Phase I	NCT01590732	[145]
	Lenalidomide	R/R lymphomas (including TCL)	Phase I/II	NCT01755975; NCT02341014; NCT02232516; NCT01755975	[146, 147]
	Alisertib	TCL cell lines, R/R aggressive B/T-cell lymphomas	Preclinical, phase I	NCT01897012	[148]
	Azatidine	CTCL cell lines and fresh Sézary syndrome cells	Preclinical		[27]
	Gemcitabine	R/R PTCL	Phase II		[150]
	Pralatrexate	TCL cell lines and a NOG murine model of TCL	Preclinical		[68]
	γ-secretase inhibitor compound E and bortezomib	A murine MT-1 model of human ATL	Preclinical		[59]
	LY2409881	Lymphoma cells	Preclinical		[60]
	Low dose localized electron beam radiation therapy (LEBT)	CTCL	Phase I		[152]
	Interferon gamma		Preclinical		[153]
	Poly ICLC, radiation	Advanced CTCL	Phase I	NCT02061449	

3.2.4 Chidamide based combination therapies

Chidamide (CS055) is a new and highly selective HDAC inhibitor, which was approved by CFDA in China for the treatment of patients with refractory and relapsed PTCL as single agent. The synergistic effect of Chidamide based combination therapies has been rarely reported. In 2017, a report about Chidamide in combination with doxorubicin in PTCL cells has been published. In this study, the synergistic effect against PTCL cells exhibited after combination treatment with Chidamide and doxorubicin, inducing more significant apoptosis, changes of mitochondrial membrane potential and H3 acetylated level [161]. In a study of evaluation of the real-world utilization of Chidamide in 383 R/R PTCL patients in China, for 127 patients receiving Chidamide combined with chemotherapy, the therapeutic effects are impressive, with an ORR of 51.18%, DCR of 74.02%, PFS of 152 days (129 days for Chidamide as single agent) and an acceptable safety profile with more than 5% patients with thrombocytopenia (18.1%), neutropenia (12.6%), anemia (7.1%), and fatigue (5.5%) [98]. The

therapeutic efficacy and safety profile of the combination of Chidamide with other targeted drugs or chemotherapy are favorable, offering an alternative choice for refractory and relapsed PTCL patients. However, the application of this combination treatment in clinic remains challenging, and further investigations are warranted.

3.2.5 Panobinostat guided combination therapies

HDAC inhibitors were reported to have synergistic antitumor activity with mTOR inhibitors based on their mechanisms of action. The combination of Panobinostat with Bortezomib exhibited highly synergistic efficacy against PTCL via inducing polyubiquitinated protein accumulation in preclinical studies, promoting its further exploration in clinical trials [162, 163]. In a phase I study of the combination of Panobinostat plus Everolimus in patients with relapsed or refractory Hodgkin and non-Hodgkin lymphoma (T-cell lymphomas included), highly synergistically therapeutic effects were demonstrated, 33% patients (indolent lymphoma, T-cell lymphoma, mantle cell lymphoma, and Hodgkin lymphoma) achieved objective responses and decreased multiple serum cytokine levels [164]. However, the adverse effects of this combination were most dose limiting severe toxicities of grade 3/4, including thrombocytopenia (64%), neutropenia (47%), anemia (20%), infection (10%), fatigue (7%), and dyspnea (7%). The promising therapeutic merits of the combination of Panobinostat with Everolimus offer new opportunities and improvements for the exploration of the Panobinostat based combination therapies against T-cell lymphomas in the future.

Paobinostat was demonstrated to have synergistic anti-lymphoma activity with proteasome inhibitor Bortezomib in many preclinical studies, advancing the clinical application in patients with relapsed or refractory peripheral T-cell lymphomas. An open-label, multicenter phase II trial of this combination was undertaken in patients with relapsed or refractory peripheral T-cell lymphoma showed that this combination therapy exhibited promising efficacy with acceptable safety and feasibility [137]. 43% patients displayed critical objective responses (including 20% complete responses). The common adverse effects of this combination therapy were grade 3/4, including thrombocytopenia (68%), neutropenia (40%), diarrhoea (20%), and asthenia or fatigue (8%), while 40% exhibited serious adverse events and 40% patients had peripheral neuropathy of any grade. The combination of Panobinostat with subcutaneous Bortezomib improved the outcomes (tolerance, treatment duration and safety profile) in patients with

relapsed multiple myeloma in a randomized phase III non-inferiority study [165]. The combination of proteasome and HDAC inhibitors demonstrated encouraging therapeutic effects and acceptable safety profile in patients with PTCL, representing a feasible and adjustable therapeutic strategy for the treatment of patients with PTCL.

Besides, the studies of combination therapy of Panobinostat with Azacitidine in acute Myeloid Leukemia and Myelodysplastic Syndromes exhibited synergestic therapeutic effects and favorable safety profile[166], implying that Panobinostat may play an important role in the treatment of a range of hematologic malignancies.

All these findings validated the promising synergistic effect of Panobinostat in combination with other agents, which offer a novel therapeutic choice for T-cell lymphoma, especially peripheral T-cell lymphoma.

Table 6. Chidamide, Panobinostat, AN-7, and MS-275 based combination therapies.

Agent1	Agent2	T-cell lymphomas	Progress	Clinical trial	Ref.
Chidamide	Chemotherapy	R/R PTCL	Phase I		[92]
	Doxorubicin	PTCL cells	Preclinical		[154]
Panobinostat	Everolimus	R/R lymphoma (including TCL)	Phase I	NCT00967044	[157]
	Bortezomib	PTCL	Phase III	NCT01023308	[129, 158]
AN-7	Doxorubicin	MF/SS cell lines, SPBL, T-cell lymphoma	Preclinical		[160]
MS-275	UVASens/UV-A photochemotherapy	CTCL Myla cell line	Preclinical		[143]

3.2.6 AN-7 guided combination therapy

Butyroyloxymethyl diethylphosphate (AN-7) is a novel HDAC inhibitor, showing selective anticancer activity in several cell lines (MF/SS cell lines and peripheral blood lymphocytes (PBL) from patients with Sézary syndrome (SPBL)) and animal models [167]. When combined with doxorubicin, more cell death was induced in both MF/SS cell lines and SPBL, but exhibited antagonistic effect in NPBL. The synergistic effect of AN-7 with doxorubicin in both MF/SS cell lines and SPBL offers promise for AN-7 as a novel HDAC inhibitor in the combinational therapy of T-cell lymphoma.

4. Perspectives

T-cell lymphomas are a heterogeneous group of lymphomas with complicate pathogenesis and poor prognosis. Novel therapeutic agents or strategies against T-cell lymphomas are urgently warranted, but with great challenges. HDACs are key epigenetic

modulators important for the biological homeostasis. The specific functions and structure make them promising drug targets. A series of HDAC inhibitors with divergent characteristics have been developed and applied in the treatment of several malignancies, many of which displayed high potency against many T-cell lymphomas, especially HTLV-1-infected T-cells, peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), and acute T-cell lymphoma (ATL). Because of the limited efficacy, safety profile, and resistance, HDAC inhibitors approved as single therapeutic agents for T-cell lymphomas are rare. To date, only Vorinostat (SAHA) for CTCL, Romidepsin for CTCL and PTCL, and Belinostat for PTCL have been approved by the FDA, and Chidamide has been approved by the CFDA for the treatment of relapsed/refractory TCL as a single agent. The application of HDAC inhibitors in the treatment of T-cell lymphomas needs diligent optimization of the structure, potency, pharmacokinetics and safety. Combination therapy employing at least two pharmaceuticals or treatments possesses many advantages over single agent therapy, such as, improved therapeutic efficacy, abated adverse effects, resistance overcome, and more therapeutic strategy optimizations based on different action of modes (mechanisms). Within the past few decades, combination therapies have been the first choice of therapeutic strategies in oncology and other diseases with complicated pathogenesis and achieved remarkable curative effects. HDACs guided combination therapies have been used in the treatment of T-cell lymphomas. And many clinical trials have been undertaken in the treatment of T-cell lymphomas, exhibiting improved therapeutic merits and acceptable adverse effects in most combination regimens of HDAC inhibitors. Although anticipated therapeutic efficacy of HDAC guided combination therapies were demonstrated in these preclinical studies and clinical trials, extensive, randomized and comparative clinical trials are needed to further evaluate the most suitable combination regimens. Besides, according to the outcomes of reported combination therapies, there are still many aspects to further optimize, such as regimens in the combination (other targeted agents, such as checkpoint inhibitors Ipilimumab [3], small PARP inhibitor PJ-34 [168] or chemotherapies or other immune therapies (antibodies against CTLA4 and PD1/PDL1 [3], BiTE Blinatumomab [6])), dosage of each regimen, dosing optimizing and administration scheduling. The precise pathogenesis of T-cell lymphomas and thorough knowledge about HDACs would help to identify novel therapeutic targets. Gene sequencing, novel genetic editing techniques [169] and application

of chemical probes in the elucidation of biomolecule functions [170] would help the understanding of drug targets in depth. De-novo drug developments or novel application of existed drugs would facilitate the flourish of HDAC inhibitors as single agent or combination regimen. Combination therapy designs should focus on optimizing the specific regimen, dosing, and administration schedule with the aim to dramatically improve synergistic therapeutic efficacy and minimize adverse effects. In all attempts to improve the therapeutic efficacy of T-cell lymphomas, the patients' status both physical (comorbidities and toxicity profile) and mental should be comprehensively evaluated. All in all, a bright future is on the way to defeat T-cell lymphomas after considering all these relevant elements and endeavor.

Abbreviations

Cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), acute T-cell lymphoma (ATL), Histone deacetylase (HDAC), nicotinamide adenine dinucleotide (NAD), tricostatin A (TSA), overall response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), adverse events (AEs), the China Food and Drug Administration (CFDA), Europe European Medical Association (EMA), uridine diphosphate glucuronosyl-transferase (UGT), multiple myeloma (MM), indolent NHL, relapsed/refractory acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), Waldenstrom's Macroglobulinemia (WM), Polycomb repressive complex 2 (PRC2), Enhancer of zeste homolog 2 (EZH2), mycosis fungoides (MF).

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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