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REVIEW

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Histone deacetylase inhibitors for leukemia treatment: current status and future directions

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Abstract

Leukemia remains a major therapeutic challenge in clinical oncology. Despite significant advancements in treatment modalities, leukemia remains a significant cause of morbidity and mortality worldwide, as the current conventional therapies are accompanied by life-limiting adverse effects and a high risk of disease relapse. Histone deacetylase inhibitors have emerged as a promising group of antineoplastic agents due to their ability to modulate gene expression epigenetically. In this review, we explore these agents, their mechanisms of action, pharmacokinetics, safety and clinical efficacy, monotherapy and combination therapy strategies, and clinical challenges associated with histone deacetylase inhibitors in leukemia treatment, along with the latest evidence and ongoing studies in the field. In addition, we discuss future directions to optimize the therapeutic potential of these agents.

Keywords Antineoplastic agents, Apoptosis, Epigenetics, HDAC inhibitor, Hematological malignancy, Histone deacetylases antagonist, Treatment resistance, Tumor microenvironment

Introduction

Leukemia arises from the uncontrolled proliferation of immature blood cells in the bone marrow and peripheral blood. Classified broadly into acute and chronic forms, leukemia is considered a multifactorial disease, involving a variety of genetic, environmental, and immunologic factors [1, 2]. Common symptoms of leukemia include fatigue, fever, easy bruising or bleeding, and recurrent infections, reflecting bone marrow failure and compromised immune function [3, 4]. Diagnosis typically involves a combination of clinical evaluation, peripheral blood smear, bone marrow aspiration, and genetic testing to subtype the disease and guide treatment decisions [5]. Despite therapeutic advances, leukemia remains a significant cause of morbidity and mortality globally, with conventional therapies, facing limitations including toxicity and risk of relapse [6].

Histone deacetylase (HDAC) inhibitors represent a class of pharmacological agents that modulate gene expression by targeting epigenetic mechanisms [7–9]. HDACs, enzymes responsible for removing acetyl groups from histone proteins, play a significant role in regulating chromatin structure and gene transcription [10, 11]. Dysregulation of HDAC activity is implicated in various diseases, including cancer, where aberrant gene expression contributes to tumorigenesis and progression [12, 13]. HDAC inhibitors exert their effects by inhibiting HDAC activity, leading to increased histone acetylation, chromatin relaxation, and transcriptional activation of genes involved in cell cycle regulation, apoptosis, and differentiation [8, 13]. Beyond histones, HDAC inhibitors can also target non-histone proteins [14]. Given their ability

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to modulate gene expression epigenetically, HDAC inhibitors have been proposed as promising therapeutic agents for a wide range of malignancies.

This review aims to provide a comprehensive clinical insight into the potential of HDAC inhibitors in the treatment of leukemia.

Main text

Mechanisms of action

In general, HDAC inhibitors exert their effects through multiple mechanisms, including:

Histone acetylation

HDAC inhibitors suppress the deacetylation of histone proteins, leading to chromatin relaxation and transcriptional activation of genes involved in cell cycle regulation, apoptosis, and differentiation [15].

Non-histone protein acetylation

HDAC inhibitors also acetylate non-histone proteins, such as transcription factors and signaling molecules, influencing various cellular processes critical for cancer pathogenesis [16].

Apoptosis induction

By upregulating pro-apoptotic genes, programmed activation of caspases, and downregulating anti-apoptotic genes, HDAC inhibitors promote apoptosis in malignant cells, leading to cell death [17–19].

Cell cycle arrest

HDAC inhibitors induce cell cycle arrest at different checkpoints, preventing uncontrolled proliferation of leukemic cells [20].

Anti-angiogenic effects

HDAC inhibitors have been shown to inhibit angiogenesis by targeting endothelial cell function and disrupting angiogenic signaling pathways, ultimately inhibiting the formation of new blood vessels in tumors [21]. HDAC inhibitors modulate the expression of genes involved in angiogenesis, such as vascular endothelial growth factor (VEGF) and its receptors, endothelial nitric oxide synthase (eNOS), and angiopoietins, through epigenetic mechanisms [22, 23]. By promoting histone acetylation and altering chromatin structure, HDAC inhibitors suppress the transcriptional activity of pro-angiogenic genes [24, 25]. Moreover, HDAC inhibitors have been shown to disrupt the tumor microenvironment by targeting stromal cells, immune cells, and extracellular matrix components, additionally impairing angiogenesis and tumor growth [26, 27].

Disruption of DNA repair mechanisms

HDAC inhibitors impair DNA repair mechanisms, enhancing the susceptibility of malignant cells to DNA damage-induced cell death [28, 29].

Autophagy induction

Previous studies have specified the autophagy-inducing role of HDAC inhibitors, generally through mTOR inhibition, NF-κB hyperacetylation, and p53 acetylation signaling pathways [30].

Classification

The classical family of HDACs are typically categorized into different classes. Each class shares a common ancestor and is characterized by structural and functional similarities [31]. The classical HDACs family is consisted of three classes [32, 33]:

- Class I: HDAC1, HDAC2, HDAC3, and HDAC8
- Class II: HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, HDAC10
- Class IV: HDAC11

Class III HDACs, also referred to as sirtuins, are structurally and mechanistically distinct. While class I and class II HDACs are zinc-dependent, class III HDACs require nicotinamide adenine dinucleotide (NAD^+) as a cofactor for their deacetylase activity, which rises from the evolutionary divergence and distinct biochemical properties of sirtuins compared to classical HDACs [34, 35].

HDAC inhibitors can also be classified into structurally diverse classes, including hydroxamic acids (such as vorinostat and panobinostat), cyclic peptides (such as romidepsin), benzamides (such as entinostat), and short-chain fatty acids (such as valproic acid). These compounds differ in their chemical structures and HDAC isoform selectivity, leading to variations in their pharmacokinetic properties and therapeutic effects.

Pharmacokinetics and clinical efficacy

The pharmacokinetic properties of HDAC inhibitors, including absorption, distribution, metabolism, and elimination, influence their bioavailability and efficacy in vivo. HDAC inhibitors are administered via various routes, including oral and intravenous, with different absorption rates and tissue distribution profiles [36]. Oral formulations of HDAC inhibitors undergo absorption in the gastrointestinal tract, where they may be subject to first-pass metabolism in the liver before reaching systemic circulation. Intravenous administration bypasses the gastrointestinal tract,

resulting in rapid and complete drug absorption into the bloodstream.

Several studies have evaluated the use of HDAC inhibitors, both as monotherapy and in combination with other agents, across various leukemia subtypes. While results have been variable, HDAC inhibitors have shown significant activity in subsets of patients, including those with relapsed or refractory disease who have failed standard therapies [37, 38]. Improved overall response rates (ORR), increased progression-free survival (PFS), and prolonged duration of response have been reported in certain trials, particularly in combination with chemotherapy or targeted agents [39, 40]. While HDAC inhibitors have demonstrated efficacy in specific leukemia subtypes, their clinical utility in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) remains under investigation [41]. Despite these encouraging findings, challenges such as drug resistance, heterogeneous patient populations, off-target effects, and optimal dosing schedules remain areas of active investigation [42, 43].

Safety

The safety profile of HDAC inhibitors in leukemia treatment is a subject of considerable interest and investigation. While HDAC inhibitors have shown promising therapeutic efficacy in preclinical and clinical studies, their clinical use could be associated with various adverse effects, including cardiac toxicity, gastrointestinal disturbances, fatigue, and hematologic toxicity [43–45]. Hematologic toxicity, in the forms of thrombocytopenia, neutropenia, and anemia, is among the most commonly reported adverse events [46]. Gastrointestinal discomfort, including nausea, vomiting, diarrhea, and loss of appetite, is also frequently observed and may require supportive care measures [36, 47, 48]. Cardiac toxicity, characterized by QT interval prolongation, T-wave flattening, ST segment depression, and arrhythmias, has been reported with specific HDAC inhibitors and underscores the importance of cardiac monitoring during therapy [43, 49]. In addition, some studies have suggested electrolyte abnormalities subsequent to administration of HDAC inhibitors as the cause of cardiac side effects [50]. Overall, further studies are required to determine the complete safety profile of HDAC inhibitors in leukemia treatment and ensure their tolerability and long-term efficacy in patients.

Clinical agents and candidates

Several agents have been proposed and studied through the last decades. Tables 1 and 2 present a comprehensive review of the preclinical and clinical studies of HDAC inhibitors. The most prominent HDAC inhibitors candidates for the treatment of leukemia are:

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, SAHA) is a broad-spectrum HDAC inhibitor that targets class I, II, and IV HDAC enzymes [51, 52]. By inhibiting these enzymes, vorinostat increases the acetylation of histone proteins, leading to the transcriptional activation of genes that induce cell cycle arrest, promote apoptosis, and inhibit tumor angiogenesis [53, 54]. This modulation of gene expression disrupts cancer cell proliferation and survival. Initially approved for the treatment of cutaneous T-cell lymphoma (CTCL), its potential has also been explored in AML and other hematological malignancies [15, 55, 56]. Studies have demonstrated its ability to synergize with other therapeutic agents, enhancing the cytotoxic effects against leukemic cells by disrupting mitochondrial function and inducing oxidative stress, which leads to apoptosis in leukemic cells [57].

Romidepsin

Romidepsin (FK228) is a selective inhibitor of class I HDACs, particularly HDAC1 and HDAC2 [58, 59]. Its anti-tumor activity is attributed to its strong induction of G2/M cell cycle arrest and activation of the intrinsic apoptotic pathway [60]. Romidepsin modifies the expression of key apoptotic regulators, enhancing the expression of pro-apoptotic proteins and suppressing anti-apoptotic proteins [61]. Primarily approved for CTCL and peripheral T-cell lymphoma (PTCL), romidepsin has been evaluated in clinical trials involving patients with various forms of leukemia [62]. Recent studies indicate the potential of romidepsin in downregulating DNA methyltransferases, leading to the demethylation of tumor suppressor genes and reactivation of their expression, thereby providing a dual epigenetic therapy approach when combined with DNA methylation inhibitors [63, 64].

Belinostat

Like vorinostat, belinostat (PXD101) is a pan-HDAC inhibitor that affects class I, II, and IV enzymes [65]. Its anticancer effects are mediated through the induction of apoptosis, cell cycle arrest, and the reduction of angiogenesis [66–68]. Belinostat also affects the acetylation of non-histone proteins critical in cell cycle regulation and apoptosis [68, 69]. While belinostat is approved for PTCL, its role in treating leukemia subtypes is under investigation. Preclinical models show that Belinostat effectively induces death in leukemic cells, particularly when combined with other chemotherapeutic or targeted agents, enhancing its antileukemic activities [68].

Table 1 Preclinical studies of histone deacetylase (HDAC) inhibitors in leukemia (non-leukemia reports also presented in the absence of sufficient studies)

HDAC class	Author (year)	Agent	Combination therapy	Cell lines	Leukemia subtype	Findings and outcomes
Hydroxamic acids	Gao et al. (2016) [131]	Vorinostat (SAHA)	Carfilzomib	MOLT-4 and HuT 78	TCL	Vorinostat, in combination with carfilzomib, showed synergistically improved anticancer effects
	Chao et al. (2015) [132]	Vorinostat (SAHA)	Vincristine	MOLT-4 and CCRF-CEM	T-ALL	Combined vorinostat and vincristine induce the pro-apoptotic pathways, resulting in significant antileukemic effects
	Young et al. (2017) [133]	Vorinostat (SAHA)	Decitabine	OCI-AML3 and HL-60	AML, APL	The combination of vorinostat and decitabine benefits from synergistically improved response and could act as a potential treatment for AML. In addition, *AXL* is a potential marker for decitabine-vorinostat treatment response
	Valdez et al. (2022) [134]	Panobinostat (LBH589)	Bisantrene, venetoclax, decitabine, and olaparib	OCI-AML3, MOLM-13, and MV4-11	AML	The combination therapy resulted in synergistic cytotoxicity in cells, damage response, and upregulation of apoptosis pathways
	Jia et al. (2019) [135]	Panobinostat (LBH589)	Sodium butyrate (HDAC inhibitor)	K-562	CML	The combination shows antileukemic effects through activation of the ERS-mediated apoptotic pathway and reduction of drug-resistance related proteins' expression
	Moreno et al. (2022) [136]	Panobinostat (LBH589)	Mercaptopurine and methotrexate	RS4;11	ALL	No synergistic effect was observed through combination therapy of panobinostat with methotrexate and mercaptopurine. However, Panobinostat monotherapy demonstrated significant antineoplastic effects
	Vagapova et al. (2021) [137]	Belinostat, hydrazostat (Belinostat-PH)	Imatinib, cytarabine, vincristine, and venetoclax	MV4-11, THP-1, HL-60, U-937, and K-562	AML, APL, CML	Hydrazostat improves the sensitivity of leukemic cells to imatinib, cytarabine, vincristine, and venetoclax
	Diamanti et al. (2007) [138]	Belinostat (PXD101)	Chemotherapy (VAD)	CCRF-CEM, MOLT-4, Jurkat, NALM6, Daudi, and Kasumi	ALL, AML	Inducing apoptosis, belinostat was effective in steroid-resistant samples, but no synergy was observed in combination therapy
	Valiuliene et al. (2015) [139]	Belinostat (PXD101)	Retinoic acid	NB4 and HL-60	APL	Belinostat demonstrated antileukemic effects through its impact on chromatin remodeling and cell growth
	Pietschmann et al. (2012) [140]	Panobinostat (LBH589)	TKI (FLT3 inhibitors: quizartinib, midostaurin, cpd.102)	MV4-11 and MOLM-13	AML	HDAC inhibitors and FLT3 inhibiting agents have significant synergistic antileukemic activity with strong induction of apoptosis even in low doses

Table 1 (continued)

HDAC class	Author (year)	Agent	Combination therapy	Cell lines	Leukemia subtype	Findings and outcomes
Cyclic peptides	Dai et al. (2008) [141]	Romidepsin (FK228)	Belinostat and bortezomib	JVM-3 and MEC-2	CLL (P-BLL)	The combination of Romidepsin and belinostat with bortezomib synergistically induces cell death in CLL cells
	Alves da Silva et al. (2022) [142]	Romidepsin (FK228)	7C6 (MICA/B antibody)	NB4, C1498, and WEHI-3	AML	Romidepsin synergizes the MICA/B inhibition properties of 7C6, suppressing the AML outgrowth through antibody-dependent phagocytosis

Table 1 (continued)

HDAC class	Author (year)	Agent	Combination therapy	Cell lines	Leukemia subtype	Findings and outcomes
Benzamides	He et al. (2020) [143]	Chidamide (CS055/HBI-8000)	Imatinib	KBM5	CML	The combination of chidamide and omatinib reduces TKI resistance and could improve the clinical outcomes of BC-CML patients
	Zhao et al. (2022) [144]	Chidamide (CS055/HBI-8000)	Apatinib	KG1α and Kasumi-1	AML	Combination therapy of chidamide and apatinib synergistically affected cell viability and induced pro-apoptotic pathways
	Hu et al. (2024) [145]	Chidamide (CS055/HBI-8000)	–	HL-60, HEL, MOLM-13, MV4-11, and Kasumi-1	AML	Affecting N6-methyladenosine-related GNAS-AS1, chidamide results in glycolysis suppression
	Gu et al. (2023) [146]	Chidamide (CS055/HBI-8000)	Cladribine	U937, THP-1, and MV4-11	AML	Affecting the HDAC2/c-Myc/RCC1 pathway, coadministration of chidamide with cladribine synergistically targets cell growth, leading to cell cycle arrest and apoptosis
	Yin et al. (2023) [147]	Chidamide (CS055/HBI-8000)	Imatinib and nilotinib	Ba/F3 P210 and Ba/F3 T315I	CML	Chidamide monotherapy can potentially overcome T315I mutation-related drug resistance through the modulation of apoptosis-autophagy pathways. Combining chidamide with TKI agents, such as Imatinib or nilotinib, increases its effectiveness
	Wang et al. (2018) [148]	Entinostat (SNDX-275, MS-275)	Cladribine	RPMI8226, U266, and MM1.R	MM	Coadministration of entinostat and cladribine induces cell cycle arrest and apoptosis, affecting the DNA damage response
	Zhou et al. (2013) [149]	Entinostat (SNDX-275, MS-275)	Vorinostat, trichostatin A, romidepsin	HL-60, MOLM-13, OCI-AML3, and OCI-AML2	AML	Entinostat, along with other HDAC inhibitors, promotes apoptosis by restoring the silenced nuclear receptors Nur77 and Nor1
	Golay et al. (2007) [150]	Givinostat (ITF2357)	–	HL-60, THP-1, U937, Kasumi, KG-1, TF-1, GFD8	AML, APL	Potent anti-leukemic activity through suppressing IL-6 and VEGF production, resulting in increased apoptosis in vitro and increased survival in vivo
	El-Khoury et al. (2014) [151]	Mocetinostat (MGCD0103) (and Valproic acid)	Flavopiridol (CKDi), chloroquine, 3-MA	MCF-7, JVM-2, and JVM-3	B-CLL	Mocetinostat induces apoptosis, along with autophagy suppression in all combination regimens

Table 1 (continued)

HDAC class	Author (year)	Agent	Combination therapy	Cell lines	Leukemia subtype	Findings and outcomes
Short-chain fatty acids	Rucker et al. (2016) [152]	Valproic acid	Chemotherapy (ICE, ATRA)	CMK, HEL, K-562, NB4, and HL-60	AML, APL	Valproic acid has shown synergistic effects in the treatment of AML when combined with intensive chemotherapy regimens

3-MA 3-Methyladenine, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia, *ATRA* all-trans retinoic acid, *BC-CML* blast crisis chronic myeloid leukemia, *B-CLL* B-cell chronic lymphocytic leukemia, *B-PLL* B-cell prolymphocytic leukemia, *CDK* cyclin-dependent kinase, *CML* chronic myelocytic leukemia, *ERS* endoplasmic reticulum stress, *FLT3* FMS-like tyrosine kinase 3, *HDAC* histone deacetylases, *ICE* idarubicin, cytarabine, etoposide, *IL* interleukin, *MICA/B* histocompatibility complex class I polypeptide-related sequence A and B, *MM* multiple myeloma, *SAHA* suberoylanilide hydroxamic acid, *T-ALL* T-cell acute lymphoblastic leukemia, *TCL* T cell lymphoma, *TKI* tyrosine kinase inhibitor, *VAD* vincristine, doxorubicin, dexamethasone, *VEGF* vascular endothelial growth factor

Table 2 Clinical studies on efficacy/safety of histone deacetylase (HDAC) inhibitors in the treatment of leukemia (non-leukemia reports also presented in the absence of sufficient studies)

HDAC class	Author (year)	Country	Trial design	Candidate	Combination therapy	Leukemia subtype	Clinical outcomes
Hydroxamic acids	Schafer et al. (2022) [153]	USA	Phase I trial	Vorinostat (SAHA)	Chemotherapy (decitabine and FLAG)	AML	With an ORR of 69% in relapsed and 38% in refractory AML, the combination of vorinostat with decitabine and FLAG-based therapies was well-tolerated and effective in this study
	Alatrash et al. (2022) [154]	USA	Phase I/II trial	Vorinostat (SAHA)	Conditioning regimen (CloFluBu)	ALL, AML, MDS	Vorinostat did not show improvement in combination with CloFluBu for leukemia patients undergoing allogeneic HSCT
	Burke et al. (2020) [155]	USA	Phase I/II trial	Vorinostat (SAHA)	Chemotherapy (decitabine, dexamethasone, vincristine, mitoxantrone, PEG-asparaginase)	B-ALL	Decitabine and vorinostat combination led to unacceptable toxicities in B-ALL
	Garcia-Manero et al. (2024) [156]	USA	Phase III trial	Vorinostat (SAHA)	Chemotherapy (cytarabine)	AML	High-dose Cytarabine during the induction therapy will not improve the AML clinical outcomes, regardless of the combination with Vorinostat
	DeAngelo et al. (2019) [157]	USA	Phase I trial	Panobinostat (LBH589)	Chemotherapy (idarubicin, cytarabine)	AML	An ORR of 60.9% with 43.5% CR and 78.3% EFS was observed
	Goldberg et al. (2020) [158]	USA	Phase I trial	Panobinostat (LBH589)	Chemotherapy (unspecified)	AML, ALL, NHL	Panobinostat was tolerated in heavily pretreated pediatric subjects. Gastrointestinal effects were observed in this study. There were no cardiac findings. There were no responses
	Wieduwilt et al. (2019) [159]	USA	Phase I trial	Panobinostat (LBH589)	Chemotherapy (7 + 3)	AML	The combination of Panobinostat with the chemotherapy was well-tolerated, with a CR/CRi rate of 32%
	Perez et al. (2021) [160]	USA	Phase II trial	Panobinostat (LBH589)	Chemotherapy (myeloablative/reduced intensity of busulfan, melphalan, and fludarabine) Tacrolimus/sirolimus for GVHD prophylaxis	ALL, AML, MDS	Panobinostat combined with standard GVHD prophylaxis resulted in a low cumulative incidence of clinically significant acute GVHD, without major adverse events, making it a safe and feasible intervention
	Gimsing et al. (2008) [161]	Denmark	Phase I trial	Belinostat (PXD101)	Chemotherapy, radiation therapy (unspecified)	CLL, MM, NHL	Belinostat is well-tolerated in patients with hematological malignancies
	Shafer et al. (2023) [162]	USA	Phase I trial	Belinostat (PXD101)	Adavosertib	AML, MDS	Coadministration of belinostat and Adavosertib is safe and feasible, but no significant clinical improvement was observed among patients
	Holkova et al. (2021) [163]	USA	Phase I trial	Belinostat (PXD101)	Bortezomib	AML, MDS	Coadministration of belinostat and bortezomib is safe and feasible, but shows limited activity in leukemic patients
	Kirschbaum et al. (2014) [164]	USA	Phase II trial	Belinostat (PXD101)	–	AML	No CR was observed among the patients, and belinostat monotherapy minimally affects AML
	Garcia-Manero et al. (2024) [165]	Multicenter	Phase III trial	Pracinostat (SB939)	Azacitidine	AML	Lack of clinical response was observed, with no significant difference reflected by adding pracinostat to the treatment protocol

Table 2 (continued)

HDAC class	Author (year)	Country	Trial design	Candidate	Combination therapy	Leukemia subtype	Clinical outcomes
Cyclic peptides	Holkova et al. (2017) [166]	USA	Phase I trial	Romidepsin (FK228)	Bortezomib	CLL/SLL, BCL, PTCL, CTCL	PR and stable disease was observed among 12.2% and 44.4% of patients, respectively. Grade III fatigue, N/V, and chills were the observed dose-limiting toxicities
	Chiappella et al. (2023) [167]	Italy	Phase Ib/II	Romidepsin (FK228)	Chemotherapy (CHOEP), SCT	PTCL	No unexpected toxicities were recorded, with an ORR of 71% and CR of 62%. Romidepsin and CHOEP combination therapy did not improve the PFS of untreated patients; however, the primary endpoint of this study was not met
	Harrison et al. (2011) [168]	Australia	Phase I/II trial	Romidepsin (FK228)	Bortezomib and dexamethasone	MM	With a 72% OR, combination therapy of romidepsin with bortezomib/dexamethasone shows significant anticancer properties with manageable toxicity
	Niesvizky et al. (2011) [169]	USA	Phase II trial	Romidepsin (FK228)	Chemotherapy, radiation therapy (unspecified)	MM	Monotherapy of romidepsin is unlikely to result in a significant objective response in refractory MM
Benzamides	Wang et al. (2020) [170]	China	Phase I/II trial	Chidamide (CS055/HBI-8000)	Chemotherapy (DCAG)	AML	The combination of chidamide and DCAG was well-tolerated and effective in relapsed/refractory AML
	Wei et al. (2023) [171]	China	Phase II trial	Chidamide (CS055/HBI-8000)	Chemotherapy (CAG), DLI	AML, MDS	With a 45% CR, 5% PR, and median OS of 19 months, the combination of chidamide with CAG and DLI is superior for post-allo-HSCT AML/MDS patients
	Shi et al. (2017) [172]	China	Phase IIb trial	Chidamide (CS055/HBI-8000)	Chemotherapy (CHOP-like regimens, platinum-containing regimens)	TCL	Median PFS was 129 vs 152 for monotherapy against combination therapy. With a 51.18% ORR, chidamide has a suitable efficacy and safety profile, and could be potentially used for refractory and relapsed PTCL patients
	Carraway et al. (2021) [173]	USA	Phase I trial	Entinostat (SNDX-275, MS-275)	Chemotherapy (Clofarabine)	ALL, ABL	The combination of entinostat with clofarabine is tolerable and effective. The impact of this combination on relapsed/refractory patients seems to be inferior to the newly diagnosed
	Bewersdorf et al. (2024) [174]	USA	Phase Ib trial	Entinostat (SNDX-275, MS-275)	Immunotherapy (Pembrolizumab)	AML, MDS	Coadministration of entinostat and pembrolizumab was related to limited clinical efficacy despite significant toxicity
	Garcia-Manero et al. (2008) [175]	USA	Phase I trial	Mocetinostat (MGCD0103)	–	AML, MDS	Mocetinostat monotherapy was proven safe and effective
	Blum et al. (2009) [176]	USA	Phase II trial	Mocetinostat (MGCD0103)	Rituximab	CLL	Mocetinostat monotherapy and combination therapy were safe. Number of patients in each intervention group is way too small to draw any conclusion on effectiveness

Table 2 (continued)

HDAC class	Author (year)	Country	Trial design	Candidate	Combination therapy	Leukemia subtype	Clinical outcomes
Short branched-chain fatty acids	Lübbert et al. (2020) [177]	Germany	Phase II trial	Valproic acid	Chemotherapy (Decitabine, ATRA)	AML	No significant superiority of OS was observed in patients receiving valproate
	Becker et al. (2021) [178]	Germany	Phase II trial	Valproic acid	Chemotherapy (Decitabine, ATRA)	AML	Valproic acid did not affect the ORR in the study groups
	Tassara et al. (2014) [179]	Germany	Phase III trial	Valproic acid	Chemotherapy (Idarubicin, cytarabine, ATRA)	AML	RFS was improved in patients receiving valproic acid; however, no significant difference was observed in EFS and OS

ABL Acute biphenotypic leukemia, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *ATRA* all-trans retinoic acid, *B-ALL* B-cell acute lymphoblastic leukemia, *BCL* B-cell lymphoma, *CAG* cytarabine, aclarubicin, GCSF, *CHOEP* cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *CLL* chronic lymphocytic leukemia, *CloFluBu* clofarabine, fludarabine, busulfan, *CML* chronic myelocytic leukemia, *CR/CRi* Complete response/incomplete count recovery rate, *CR* complete remission, *CTCL* cutaneous T-cell lymphoma, *DCAG* decitabine, cytarabine, aclarubicin, GCSF, *DLI* donor lymphocyte infusion, *EFS* event-free survival, *FLAG* fludarabine, cytarabine and GCSF, *GCSF* granulocyte colony-stimulating factor, *GDP* gemcitabine, dexamethasone and cisplatin, *GVHD* graft-versus-host disease, *HCT* hematopoietic cell transplantation, *HDAC* histone deacetylase, *HSCT* hematopoietic stem cell transplantation, *ICE* idarubicin, cytarabine, etoposide, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *N/V* nausea and vomiting, *NHL* non-Hodgkin lymphoma, *OR* overall response, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* patrial remission, *PTCL* peripheral T-cell lymphoma, *RFS* relapse-free survival, *SAHA* suberoylanilide hydroxamic acid, *SCT* stem cell transplantation, *SLL* small lymphocytic lymphoma, *TCL* T cell lymphoma, *VAD* vincristine, doxorubicin, dexamethasone

Panobinostat

Panobinostat (LBH589) inhibits class I, II, and IV HDAC enzymes, which results in a more robust increase in histone acetylation compared to other HDAC inhibitors [15, 70]. This extensive hyper-acetylation disrupts many cellular processes in cancer cells, including gene expression, cell cycle progression, and survival pathways. Initially approved for multiple myeloma (MM) in 2015, panobinostat has demonstrated significant potential in preclinical studies for the treatment of ALL [71–73]. It has been shown to induce apoptosis and enhance the efficacy of other therapeutic agents like bortezomib through synergistic mechanisms in leukemic cells [74]. Furthermore, panobinostat has been involved in clinical trials aimed at evaluating its effectiveness in overcoming drug resistance and preventing disease relapse in leukemia patients [75].

Chidamide

Chidamide, also known as CS055/HBI-8000, is a novel benzamide class HDACi that has shown promising activity in preclinical models and clinical trials for the treatment of leukemia [76, 77]. Chidamide selectively inhibits class I HDACs (HDAC1, 2, 3, and 10), leading to increased histone acetylation and modulation of gene expression [78, 79]. Chidamide has demonstrated anti-leukemic activity in preclinical and clinical studies, particularly in patients with relapsed or refractory disease [80, 81]. Combination therapy strategies, administrating chidamide along with chemotherapy agents or targeted therapies, are being explored to enhance therapeutic efficacy and overcome drug resistance.

Entinostat

Entinostat, (MS-275, SNDX-275), is a synthetic benzamide derivative that selectively inhibits class I HDAC [82]. Preclinical studies have demonstrated the ability of entinostat in the induction of cell cycle arrest and expression of pro-apoptotic proteins in leukemic cells [83]. Recent clinical trials evaluating entinostat as monotherapy or in combination with other agents have shown promising results in leukemia patients, including those with AML and chronic lymphocytic leukemia (CLL) [84, 85]. Combining entinostat with hypomethylating agents such as azacitidine has been extensively studied as a potential treatment regimen for leukemia patients [85, 86].

Mocetinostat

Mocetinostat (MGCD0103) is a highly selective inhibitor of class I and IV HDAC isoforms that has demonstrated preclinical activity against leukemia cells [87, 88]. Mocetinostat also establishes antileukemic effects through the induction of apoptosis, cell cycle arrest, and modulation of gene expression. Clinical studies of mocetinostat in the treatment of leukemia are still ongoing, and the results are indefinite to date.

Givinostat

Givinostat (ITF2357) is a hydroxamic acid derivative inhibiting class I and IIb HDAC isoforms [89]. Givinostat has demonstrated preclinical activity in leukemia models, including the induction of apoptosis and differentiation of leukemic cells [90, 91]. Clinical studies investigating givinostat in leukemia patients, particularly those with AML and myelodysplastic syndromes (MDS), are ongoing, evaluating the patients' hematologic responses and improvements in disease-related symptoms.

Other candidates

Several other candidates are being studied preclinically, including fimepinostat (CUDC-907), ivaltinostat (CG-200745), and CUDC-101, which are chiefly studied for solid tumors, but also considered for relapsed/refractory hematologic malignancies [42, 92–94].

Repurposed agents

Due to the heterogenic spectrum of HDAC classes, the development of novel HDAC-targeting agents has been challenging, which has led to frequent endeavors to repurpose the currently available drugs [95, 96]. Trichostatin A is an antibiotic antifungal agent with specific class I and II HDAC inhibitory properties, which has also demonstrated significant anti-leukemic effects in preclinical studies [97–99]. Apicidin is another fungal metabolite with HDAC inhibitory properties, which has been proven to induce pro-apoptotic activities in hematological malignancies [100, 101].

In addition, some distant agents, such as valproic acid—which is primarily used as an antiepileptic medication—have also shown HDAC inhibitory activities [102, 103], which, although might not be a primary choice of cancer treatment, have demonstrated strong evidence for positive antileukemic effects in combination with novel and conventional cancer therapies [104].

Combination therapies

Several studies have proposed therapeutic regimens of HDAC inhibitors combined with other treatment modalities in order to overcome resistance, minimize off-target effects, and increase the clinical efficacy for the treatment of leukemia subtypes [105]. As displayed in Fig. 1, these combination regimens can synergistically enhance antitumor effects and improve patient outcomes. Several combination protocols are being studied, the main of which being:

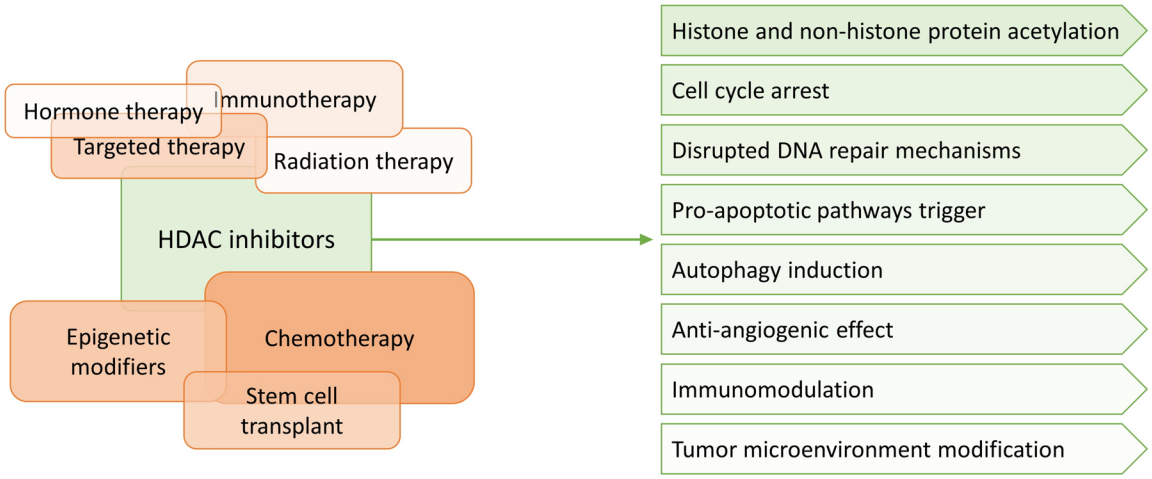

Fig. 1 HDAC inhibitors exhibit antileukemic effects, either as monotherapy or in combination with other treatment modalities

Combination with chemotherapeutic agents

Combining HDAC inhibitors with conventional cytotoxic chemotherapy agents is a rational approach to enhance tumor cell destruction and overcome chemotherapy resistance [106]. Preclinical studies have demonstrated synergistic interactions between HDAC inhibitors and agents, such as cytarabine, doxorubicin, and vincristine in leukemia models, leading to activation of pro-apoptosis pathway and cell cycle arrest in leukemic cells [107]. Clinical trials evaluating the combination of HDAC inhibitors with chemotherapy regimens in leukemia patients have shown promising results, including improved response rates and survival outcomes, mostly with acceptable toxicity levels (Table 2).

Combination with immunotherapy

HDAC inhibitors can modulate the tumor microenvironment, enhance antigen presentation, and promote anti-tumor immune responses [108–110]. Previous studies suggested a significant synergistic effect for the coadministration of HDAC inhibitors and immunomodulating agents in solid tumors, with potentially high levels of toxicity [111]. However, the studies on hematological malignancies are still indefinite. Considering the rapidly evolving landscape of cancer immunotherapy, further studies are required to determine the effectiveness and safety of these combinations, particularly in treatment regimens involving immune checkpoint inhibitors and tumor microenvironment components, such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) [112, 113].

Combination with targeted therapies

Combining HDAC inhibitors with tyrosine kinase inhibitors (TKIs) targeting aberrant signaling pathways such as FLT3, BCR–ABL, or JAK–STAT has shown promise in preclinical models of leukemia, leading to enhanced apoptosis and inhibition of leukemic cell proliferation [114–116]. Gilteritinib, midostaurin, sorafenib, and quizartinib are among the most common FLT3-inhibiting agents combined with HDAC inhibitors for leukemia treatment [117, 118].

Combination with radiation therapy

In general, radiation therapy is not the primary treatment strategy for leukemia. However, combining HDAC inhibitors with radiation therapy has the potential to enhance the efficacy of palliative radiotherapy and overcome tumor resistance mechanisms in the treatment of leukemia metastases. The rationale behind this combination lies in the ability of HDAC inhibitors to modulate chromatin structure, sensitize tumor cells to radiation-induced DNA damage, and promote apoptotic cell death [119]. HDAC inhibitors alter the chromatin structure and DNA repair mechanisms, leading to increased sensitivity of metastatic cells to ionizing radiation-induced DNA damage (radiosensitization), thereby enhancing the cytotoxic effects of radiation therapy [120]. In addition, HDAC inhibitors induce apoptosis through multiple mechanisms, which synergize with radiation-induced apoptosis. Moreover, the anti-angiogenesis effects of HDAC inhibitors enhance the efficacy of radiation therapy by reducing tumor blood supply and oxygenation to metastatic tumor cells [121]. However, the current

Table 3 Ongoing trials on the safety and effectiveness of histone deacetylase (HDAC) inhibitors in treatment of leukemia (clinicaltrials.gov)

Trial ID	Country	Study design	Study population	Interventions
NCT03843528	USA	Dose-finding phase I trial	Children (< 21) undergoing allogeneic HCT for Myeloid Malignancies (AML, MDS, JMML, MPAL)	Vorinostat in combination with low-dose azacitidine
NCT00392353	USA	Phase I/II trial	Adult patients with MDS or AML	Vorinostat, in combination with 5AC
NCT03842696	USA	Phase I/II multicenter trial	Children, adolescents, and young adults undergoing allogeneic BMT (GVHD prophylaxis)	Vorinostat and tacrolimus (or cyclosporine), methotrexate, MMF, cyclophosphamide
NCT05317403	USA	Phase I trial	Pediatric and young adult patients relapsed and refractory AML	Vorinostat, venetoclax, and 5AC, in addition to cytarabine, fludarabine, and filgrastim
NCT01522976	USA, Canada	Randomized phase II/III trial	Higher-risk MDS and CMML adult patients	5AC alone or in combination with lenalidomide or vorinostat
NCT02386800	International	Open-label, multicenter, phase IV trial	Adult/pediatric patients with prior completed global Novartis or Incyte-sponsored studies (Myelofibrosis, PV, GVHD, AML, thalassemia)	Panobinostat and ruxolitinib
NCT02506959	USA	Phase II trial	Adult patients with refractory/relapsed Myeloma	Panobinostat with high-dose gemcitabine/busulfan/melphalan with ASCT
NCT03772925	USA	Multicenter phase I trial	Relapsed/refractory AML/MDS adult patients	Pevonedistat and belinostat
NCT02737046	USA	Phase II trial	Adult patients with ATL	Belinostat in combination with zidovudine, interferon-Alfa-2b, pegylated interferon-alfa
NCT02787369	USA	Phase Ib trial	Adult patients with relapsed CLL	Ricolinostat (ACY-1215), in combination with ibrutinib and idelalisib
NCT01638533	USA, Canada	Phase I trial	Adult patients with lymphomas, CLL, and selected solid tumors	Romidepsin
NCT03564470	China	Open-label, multicenter phase II/III trial	Adult Ph-like ALL patients	Chidamide and dasatinib
NCT05881265	China	Multicenter phase II trial	Patients with ATRA- and Arsenic-resistant APL	Chidamide and venetoclax
NCT06220487	China	Open-label single-arm phase II trial	Patients with newly diagnosed Philadelphia chromosome-positive ALL	Chidamide with prednisone, olverembatinib, and blinatumomab
NCT01305499	USA	Randomized phase II trial	Elderly patients with AML	Entinostat, in combination with 5AC
NCT02553460 (TINI I)	USA, Canada	Phase I/II trial	Infants with ALL	Total therapy (vorinostat, ITMHA, dexamethasone, mitoxantrone, pegaspargase, asparaginase erwinia, chrysanthemi, bortezomib, cyclophosphamide, mercaptopurine, methotrexate, leucovorin calcium, cytarabine, etoposide, vincristine)
NCT05848687 (TINI II)	USA	Phase I/II trial	Infants with ALL	Total therapy (vorinostat, with dexamethasone, mitoxantrone, PEG asparaginase, bortezomib, mercaptopurine, methotrexate, blinatumomab, and ziftomenib)
NCT03117751 (TINI XVII)	USA, Australia	Phase I/II trial	Infants with ALL	Total therapy (vorinostat, prednisone, vincristine, daunorubicin, pegaspargase, erwinase®, cyclophosphamide, cytarabine, mercaptopurine, dasatinib, methotrexate, blinatumomab, ruxolitinib, bortezomib, dexamethasone, doxorubicin, etoposide, clofarabine, idarubicin, nelarabine, thioguanine, asparaginase erwinia chrysanthemi (recombinant)-rywn, calaspargase pegol)

5AC 5-Azacitidine, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia, *ASCT* autologous stem cell transplant, *ATL* adult T-cell leukemia/lymphoma, *ATRA* all-trans retinoic acid, *BMT* blood and marrow transplantation, *CML* chronic myelocytic leukemia, *CMML* chronic myelomonocytic leukemia, *GVHD* graft versus host disease, *HCT* hematopoietic cell transplantation, *ITMHA* intrathecal methotrexate, hydrocortisone, and cytarabine, *JMML* juvenile myelomonocytic leukemia, *MDS* myelodysplastic syndrome, *MMF* mycophenolate mofetil, *MPAL* mixed-phenotype acute leukemia, *Ph-like* Philadelphia chromosome-like, *PV* polycythemia vera

evidence regarding the clinical applicability of this combination strategy is limited.

Combination with other epigenetic modifiers

Combining HDAC inhibitors with other epigenetic modifiers, such as DNA methyltransferase (DNMT) inhibitors or bromodomain and extra-terminal (BET) protein inhibitors, could modulate multiple layers of epigenetic regulation and achieve synergistic antitumor effects [122–124].

DNMT inhibiting azacitidine and decitabine are among the common hypomethylating agents, recommended for leukemia combination therapy with HDAC inhibitors [125]. A recent preclinical study has demonstrated that combining decitabine and HDAC inhibition resulted in significant downregulation of both oncogenes and the epigenetic modifiers often overexpressed in leukemia [126]. Preclinical studies have also confirmed that combining HDAC inhibitors with DNMT inhibiting agents or BET inhibitors could lead to an enhanced reprogramming of gene expression, induction of differentiation, and inhibition of leukemic cell proliferation [127, 128]. Clinical trials investigating the combination of HDAC inhibitors with epigenetic modifiers in leukemia patients are still ongoing, aiming to assess safety, efficacy, and potential biomarkers of response.

Ongoing research

Several trials are currently ongoing to determine the effectiveness and safety of HDAC inhibitors in the treatment of leukemia. Most of the ongoing studies focus on adding HDAC inhibitors as an arm of a combined protocol for treating leukemia [129, 130]. Table 3 summarizes the ongoing trials of HDAC inhibitors monotherapy and combination therapy for leukemia treatment.

Future directions

Future research endeavors regarding the potential of HDAC inhibitors in the treatment of leukemia should address the following issues:

- Combination therapies: The synergistic effects of HDAC inhibitors with available novel and conventional cancer therapies, including other targeted agents, chemotherapy, and immunotherapy, in order to improve efficacy and minimize resistance.
- Biomarker identification: Identifying predictive biomarkers for response to HDAC inhibitor therapy, in order to select leukemia patients who are most likely to benefit from HDAC inhibitor therapy and monitoring treatment response.
- Epigenetic profiling: Utilizing epigenetic profiling to stratify leukemia patients based on their epigenetic signatures and tailor treatment approaches accordingly.
- Developing next-generation HDAC inhibitors: Designing selective HDAC inhibitors with improved potency, pharmacokinetics, and safety profiles to overcome limitations associated with current agents.
- Immunomodulatory effects: Exploring the immunomodulatory effects of HDAC inhibitors, including their impact on the tumor microenvironment and immune checkpoint regulation, to enhance antileukemic immune responses.

Conclusion

Histone deacetylase inhibitors represent a promising therapeutic strategy for different leukemia subtypes by targeting epigenetic dysregulation implicated in leukemogenesis. While significant progress has been made in understanding their mechanisms of action and clinical efficacy, challenges such as drug resistance and life-limiting side effects still persist. Ongoing research efforts focused on combination therapies, biomarker identification, and next-generation HDAC inhibitors hold promise for improving outcomes in patients with hematological malignancies.

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MSH: Conceptualization, data curation, visualization, writing—original draft. ZS: data curation, writing—review & editing. MAA: data curation, writing—original draft. YVG: data curation, writing—original draft. MA: visualization, writing—review & editing.

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