Clinical Epigenetics

REVIEW

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Advances in epigenetic treatment of adult T-cell leukemia/lymphoma: a comprehensive review

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Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1) infection causes the uncommon and deadly cancer known as adult T-cell leukemia/lymphoma (ATLL), which affects mature T cells. Its clinical appearance is varied, and its prognosis is often miserable. Drug resistance to conventional therapies confers significant therapeutic challenges in the management of ATLL. This review discusses the emerging role of epigenetic medical advances in the treatment of ATLL, focusing on DNA methyltransferase inhibitors, histone deacetylase inhibitors, histone methyltransferase inhibitors, and BET inhibitors. Indeed, several classes of epigenetic therapies currently exhibit trailed efficacy in preclinical and clinical studies: DNA methyltransferase inhibitors like azacitidine and decitabine reexpression of silenced tumor suppressors; histone deacetylase inhibitors like vorinostat and romidepsin induce cell cycle arrest and apoptosis; bromodomain and extra-terminal inhibitors like JQ1 disrupt oncogenic signaling pathways. Whereas preclinical and early clinical data indicate modest to good efficacy for such treatments, significant challenges remain. Here, we discuss the current state of understanding of epigenetic dysregulation in ATLL and appraise the evidence supporting the use of these epi-drugs. However, despite the opened doors of epigenetic treatment, much more research is required with regard to showing the best combinations of drugs and their resistance mechanisms, the minimization of adverse effects, and how this hope will eventually be translated into benefit for the patient with ATLL.

Keywords ATLL, Epigenetic treatment, DNA methylation, Histone modification, DNMTi, HDACi, HMTi

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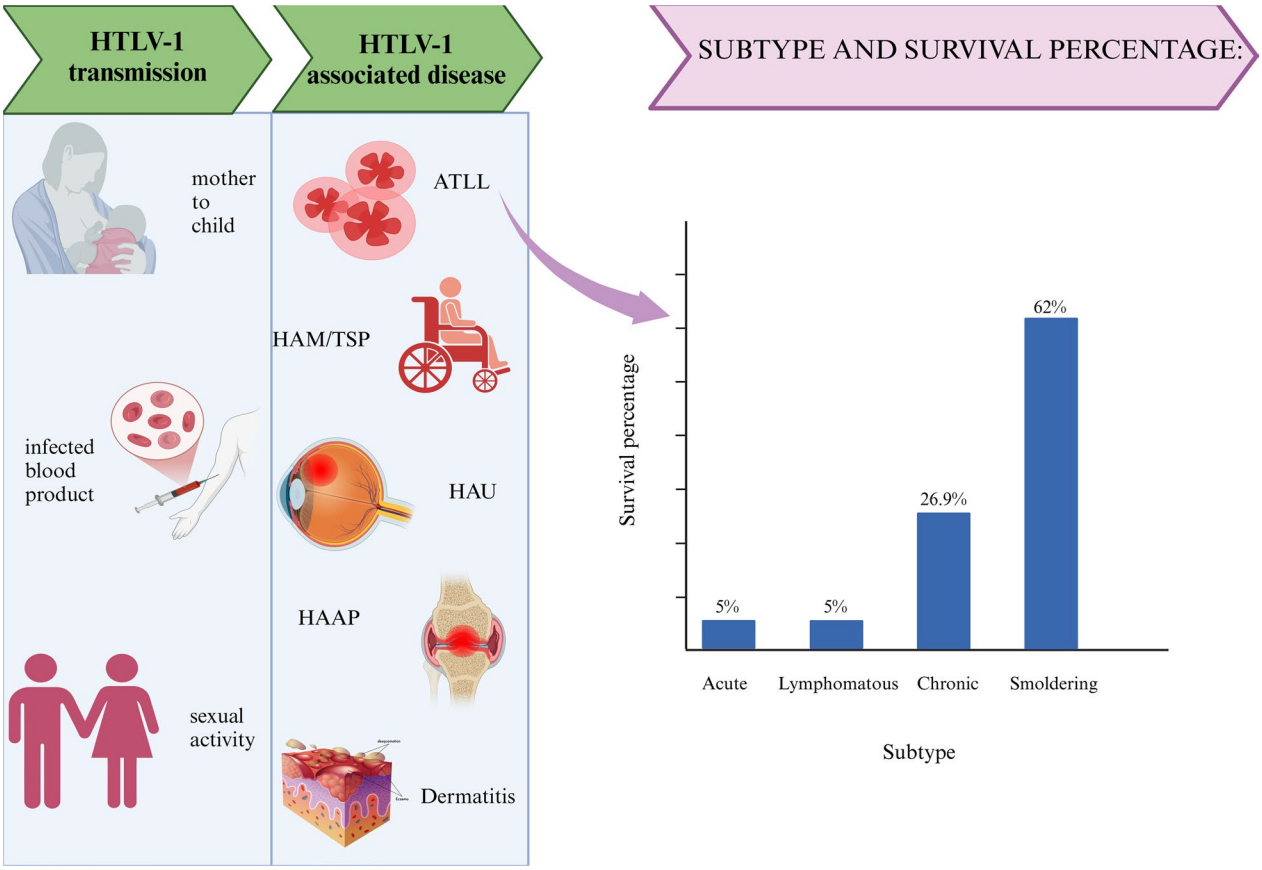

Fig. 1 HTLV-1 transmission and associated disease (created with biorender)

Introduction

The complex retrovirus known as HTLV-1, or human T-lymphotropic virus type 1, mainly infects CD4+ T cells, although it can also infect dendritic cells, endothelial cells, monocytes, and CD8+ cells. Its genome includes pol, env, pro, gag, and a number of essential genes, including those in the pX region. Six viral auxiliary proteins—Basic Zipper Factor (HBZ), p13II/p8, p30II, p12I, Tax, and Rex—are encoded by these genes. HTLV-1 infects many organs and is spread through unprotected intercourse, injectable medication usage, organ transplants, and blood transfusions. Adult T-cell leukemia/lymphoma (ATLL) and HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) are two serious illnesses brought on by HTLV-1 (Fig. 1) [1, 2]. There are four subtypes of ATLL, a CD4+ T-cell malignancy: acute, chronic, smoldering, and lymphoma. The most prevalent and severe variety is the acute form. ATLL presents with non-Hodgkin's lymphoma-like symptoms (e.g., fever, lymphadenopathy, organomegaly, jaundice, fatigue, weight loss, and infections) and skin manifestations. They fall into six groups: purpuric, erythrodermic, patch, plaque, multipapular, and nodulotumoral. These skin symptoms have predictive value and may be the initial indication of the illness (Fig. 1) [3–6].

Some of the current treatment approaches for ATLL include targeting surface molecules, monoclonal antibodies, interferon therapy, chemotherapy, and stem cell transplantation [1].

Much importance has been given to the study of epigenetic changes in cancer, a field arising from several interdisciplinary interests [7].

Nonetheless, epigenetic changes are reversible heritable changes induced by environmental factors. As such, they play a critical role in tumor development or are promising targets for therapies [8].

External factors drive epigenetic changes and reversible modifications and represent the main driving force underlying tumorigenesis; thus, they constitute an appealing target for therapy. "Epi-drugs" aimed at targeting these alterations have been developed during the last 40 years and reached clinical trials with some success, leading to FDA approval of several types. These treatments can affect energy metabolism, affecting several genes and proteins, and induce cell

differentiation, cell cycle arrest, and cell death. Since epigenetic modifications are essentially reversible, they are great therapeutic intervention possibilities [8–11].

The use of combination treatments of epi-drugs with chemotherapy or immunotherapy has so far resulted in improved tumor remission, reduced chemoresistance, increased life expectancy, and decreased side effects for patients. Epi-drugs are helpful as a single treatment or in combination because they may improve anti-tumor effects, overcome drug resistance, and activate the tumor's immune response. This method can also make low dosages of standard chemotherapy possible because of a further consequent reduction in side effects and an increase in the quality of patients' lives [8–10].

Epigenetic therapy efficiently acts as a treatment strategy for various malignancies [7].

After establishing the importance of epigenetic mechanisms in the pathogenesis of diseases, we focus on the therapeutic role of epigenetic drugs in the context of ATLL. Next, certain epigenetic agents that have shown efficiency in targeting ATLL cells and modifying disease outcomes will be discussed.

Epigenetic alternation in ATLL

Epigenetic mechanisms such as DNA methylation, histone modifications, nucleosome positioning, and chromatin looping play pivotal roles in regulating HTLV-1's transcription and contributing to its pathogenesis [12].

EP300 and its homolog CBP transcriptionally co-activate genes involved in various cellular functions, such as DNA repair, apoptosis, differentiation, and proliferation. Most recently, Northern American individuals with adult T-cell leukemia/lymphoma (ATLL) were found to have somatic hypermutations in EP300 (but not CBP) [13].

Epigenetic regulator mutations are more common in North American ATLL (NA-ATLL), especially in EP300, which is mutated in 20% of patients [14]. Reduced p53 levels are linked to EP300 mutations [15].

These mutations cause ATLL cells to experience replication stress and genomic instability, particularly during S-phase [13].

Additionally, research has shown that ATLL patients had hypermethylation in several cell cycle regulatory genes, such as p15INK4b, p16INK4a, and p14ARF [16].

Epigenetic changes contribute significantly to the development of ATLL by deactivating tumor suppressor genes, which are crucial for preserving genetic and genomic integrity. These changes impair cell adhesion, DNA damage response, apoptosis mechanisms, and control over cellular proliferation [17].

Tax interacts with methyl-CpG-binding domain 2 (MBD2) to stimulate transcription from a highly methylated HTLV-1 LTR [18].

HTLV-1 provirus represents hypomethylation within the plus-strand promoter for the viral proteins that are expressed with Tax [19].

Histone modifications, such as H3K4me3, H3K9Ac, and H3K27Ac, are dynamic and highly correlated with the expression of HTLV-1 plus-strand. These histone modifications are all linked to transcriptional repression and chromatin condensation, contributing to the silencing of genes that would typically limit cell proliferation, promote apoptosis, or maintain genomic stability; therefore, these histone modifications participate in the regulation of viral transcription [12, 19, 20].

One of the modifications often reprogrammed in ATLL cells is the trimethylation at histone H3Lys27 via polycomb-repressive complex 2, which influences regulation at the level of gene expression and progresses the disease [21].

Epigenetic treatment

The field of pharmaco-epigenomics is also developing at present, considering the targeting of epigenetic marks for therapy with implications in cancer [9].

This therapeutic strategy can be used either alone or in conjunction with other therapies, such as immunotherapy or chemotherapy, to improve the

Table 1 An overview of clinical DNMTi, their mechanism, clinical status, and their effect on ATLL

DNMTi	Mechanism of action	Clinical trial status	Efficacy level in ATLL	References
5-Azacytidine (5azaC)	Tumor size reduction, increased survival, and cellular differentiation	Phase I, II, III, FDA approved	High efficacy (strong evidence)	[37–40]
5-Aza-2′-deoxycytidine (5azadC) (Decitabine)	Anti-tumor effects include inhibition of cell growth and induction of cell death. At lower concentrations, reduced DNA methylation; at higher concentrations, induction of cell death	Phase I, II, III, FDA approved	High efficacy (strong evidence)	[41, 41–44]
Guadecitabine (SGI-110)	Anti-tumor effects	Phase I, II, III	Not Evaluated	[38, 45]
MG98	Inhibition of tumor growth and reactivation of the P16 gene	Phase I (completed)	Not Evaluated	[38, 46, 47]

Table 2 An overview of pre-clinical DNMTi, their mechanism, clinical status, and their effect on ATLL

DNMTi	Mechanism of action	Clinical trial status	Efficacy level in ATLL	References
Zebularine	Increased tumor sensitivity to treatment and induction of apoptosis	Pre-clinical	Not evaluated	[38, 48, 49]
SGI-1027	Reactivation of tumor suppressor genes and moderate pro-apoptotic effects	Preclinical	Not evaluated	[38, 50, 51]
DC_05 analogues	Inhibition of DNMT1 and induction of cell death	Preclinical	Not evaluated	[38, 52]
Quinazoline derivatives	Inhibition of cell proliferation	Preclinical	Not evaluated	[38, 53]
Propiophenone derivatives	Inhibition of cell proliferation	Preclinical	Not evaluated	[38, 54]
Procainamide conjugates	Selective cytotoxicity toward DNA methyltransferases	Preclinical	Not evaluated	[38, 55]
Indole derivatives	Inhibition of cell proliferation	Preclinical	Not evaluated	[38, 56]
Isoxazoline and oxazoline derivatives	Inhibition of cell proliferation	Preclinical	Not evaluated	[38, 57, 58]
Dichlone	Cytotoxicity	Preclinical	Not evaluated	[38, 59]
RG108 analogues	Greater cytotoxicity than RG108	Preclinical	Not evaluated	[38, 60, 61]
SW155246	Reactivation of the RASSF1A gene	Preclinical	Not evaluated	[38, 62]
Nanaomycin A	Reactivation of tumor suppressor genes	Preclinical	Not evaluated	[38, 63]
Laccaic acid A	Up-regulation of VGF and MAL genes	Preclinical	Not evaluated	[38, 64]
Flavonoid derivatives (Kazinol Q, chloronitroflavanones	Inhibition of cell proliferation and reactivation of the E-cadherin gene	Preclinical	Not evaluated	[65, 38, 66]
Indole-3-carbinol	Inhibition of tumor growth	Investigational	High efficacy (strong evidence)	[67]

anti-tumor effect, overcome medication resistance, and stimulate immune responses [10, 22].

Patients with ATLL in North America have a unique genomic landscape with frequent epigenetic alterations, especially in EP300, which are linked to a poor prognosis [14].

In preclinical and clinical trials, epigenetic treatments for ATLL and ALL have shown promise, including DNA methyltransferase inhibitors and histone deacetylase inhibitors (HDIs) [14, 23].

Histone methylation, histone demethylation, histone deacetylation, and DNA methylation inhibitors are examples of epi-drugs [24].

DNMT inhibitors (DNMTIs)

Tumour tissues frequently overexpress DNA methyltransferases (DNMT), particularly DNMT1, DNMT3A, and DNMT3B, which aid in the expression of tumor suppressor genes [25]. Establishing and maintaining the DNA methylation pattern is the responsibility of DNMT1, DNMT3A, and DNMT3B [26]. The downregulation of KLF4 expression has been linked to the hypermethylation of the KLF4 promoter, which is mediated by DNA methyltransferases (DNMTs), specifically DNMT1 [27]. Also, DNMTs can cause hypermethylation in the EGR3 gene [28].

Hypermethylation of KLF4 and EGR3, among other specific genes in ATLL, increases throughout disease development. The silencing of these genes through methylation allows the cells of ATLL to evade apoptosis and activation-induced cell death [29]. Inhibition of DNMTs has transformed into one of the most promising methods in cancer treatment, and different DNMT inhibitors were developed [30]. Those inhibitors can be classified into two groups: nucleoside analogs and non-nucleoside inhibitors [31].

Nucleoside analogs like Decitabine and zebularine integrate into DNA and interfere with methylation processes through various mechanisms [32]. Non-nucleoside inhibitors are synthetic compounds such as hydralazine and RG108 as well as natural compounds including curcumin and genistein that inhibit DNMTs through multiple mechanisms [30]. Of late, paradoxically, in some CpG sites, DNMTi exhibits increases in methylation, which indeed affects cancerous cell proliferation and pathways of induced apoptosis [33]. Zebularine is a more stable cytidine analog that has shown potential, but there has been no recent clinical data [34]. These medications work by blocking DNMTs, which causes previously inactive tumor suppressor genes to become active again [30]. The mechanisms of action include epigenetic changes and induction of apoptosis [35]. Other DNMT inhibitors include nucleoside analogs SGI-110 and CP-4200 and non-nucleoside inhibitors, synthetic hydralazine, RG108, and natural curcumin, EGCG [30, 36] (Tables 1, 2).

Learning their pharmacological properties, cellular interactions, and mode of action are essential in optimizing clinical efficacy [35].

To date, two FDA-approved DNMTi, azacitidine and Decitabine, show clinical efficacy in hematologic malignancies with limited activity against solid tumors [68, 69].

Azacytidine and Decitabine are two cytosine analogous molecules applied in the epigenetic treatments of cancers. They work mainly as DNA methyltransferase inhibitors. Both agents can indeed induce DNA hypomethylation, but their modes of action differ [35]. Decitabine's effects more clearly relate to DNA demethylation and cell cycle advancement, particularly in S-phase [70]. AZA acts more globally, inhibiting RNA methylation on DNMT2 target sites, which could impact RNA metabolism [71].

Between the two, AZA demonstrated greater potency in non-small cell lung cancer cell lines, inducing more pronounced DNA damage and apoptotic markers. The drugs also exhibited distinct effects on gene expression patterns and cell cycle dynamics, with AZA leading to sub-G1 phase accumulation and DAC(decitabine) promoting an increase in G2/M phase cells [72]. Such differences emphasize the complex and multifaceted nature through which these drugs exert their anticancer effects.

In general, the pathophysiology of ATLL may be significantly influenced by DNA hypermethylation. By adding DNA hypomethylating agents, the hypermethylated subgroups in T-ALL and ATLL have generated groups with poor outcomes [73, 74]. Two studies demonstrate frequent genomic loss of p16INK4a (CDKN2A) in Adult T-cell Leukemia/Lymphoma (ATLL). The first investigated CDKN2 gene alterations in ATLL, explicitly focusing on homozygous deletions, finding these alterations more frequent in patients with acute ATLL compared to indolent subtypes. The second study, using SNP array karyotyping on 426 samples, identified significantly recurrent focal losses, including those in CDKN2A. These findings support the frequent loss of function of the tumor suppressor gene p16INK4a in ATLL [75, 76].

DNA demethylating agents such as 5-azacytidine and Decitabine promoted gene re-expression and inhibited tumor growth in treating hypermethylated T-ALL and ATLL [37, 73].

Novel oral demethylating agents, such as OR-2100, have demonstrated anti-ATLL activity with less hematotoxicity compared to Decitabine. These agents target the aberrant DNA methylation that affects genes in T-cell receptor signaling and other critical pathways for the tumorigenesis of ATLL [41].

Decitabine and its new prodrugs, OR-1200 and OR-2100 (OR21), show promise for ATLL treatment by targeting abnormal DNA hypermethylation, which contributes to the growth of HTLV-1-infected cells [41]. These compounds reduce cell growth through global DNA hypomethylation in xenograft tumors, with OR21 causing less hematotoxicity compared to Decitabine [41, 74].

It has been reported that DNA methylation in hypermethylated sites strongly correlates with the development and progression of ATLL [41]. Decitabine has a selective effect in the EP300-mutated ATLL samples, therefore showing a targeted therapy [14].

Resistance to DNA demethylating agents in ATLL cells can arise from the misregulation of enzymes critical to pyrimidine metabolism, such as deoxycytidine kinase and uridine cytidine kinase 2 [77]. From that perspective, targeting aberrant DNA methylation is still considered one of the promising therapeutic approaches for ATLL, thus opening new horizons for novel treatment of this aggressive hematological malignancy [41, 78].

Histone deacetylase inhibitors (HDACIs)

Histone deacetylase inhibitors (HDACIs) have demonstrated potential as effective anticancer agents by reactivating tumor suppressor genes and promoting selective apoptosis in cancer cells [79, 80]. HDACIs induce the acetylation of histones, which results in a decompaction of the chromatin structure and increased gene transcription (Fig. 2) [81]. These compounds also affect non-histone proteins, thereby modulating genes associated with cell cycle, apoptosis, and angiogenesis (Fig. 2) [80]. Importantly, HDACIs have minimal toxicity in normal tissues, hence carrying great potential as therapeutic agents [82]. Further research has been directed at several combination regimens of HDACIs with other anti-cancer drugs to enhance their therapeutic potential [81, 83].

HDACIs are an exciting new class of anticancer therapeutics and can broadly be divided into five classes: hydroxamic acids, cyclic tetrapeptides, short-chain fatty acids, benzamides, and electrophilic ketones [84]. Hydroxamic acid-based HDACIs, such as vorinostat, chelate the zinc ion in the HDAC catalytic sites through the hydroxamic acid moiety in a way that provides very effective inactivation of these enzymes [85]. Such compounds have been helpful against both hematologic cancers and solid tumors, with a number currently in clinical trials and some already FDA-approved [86]. All these HDACIs are being studied either individually or in combination with other anticancer therapies for their potential in treating various hematological cancers and solid tumors [86, 87]. A summary of HDAC inhibitors is shown in Table 3.

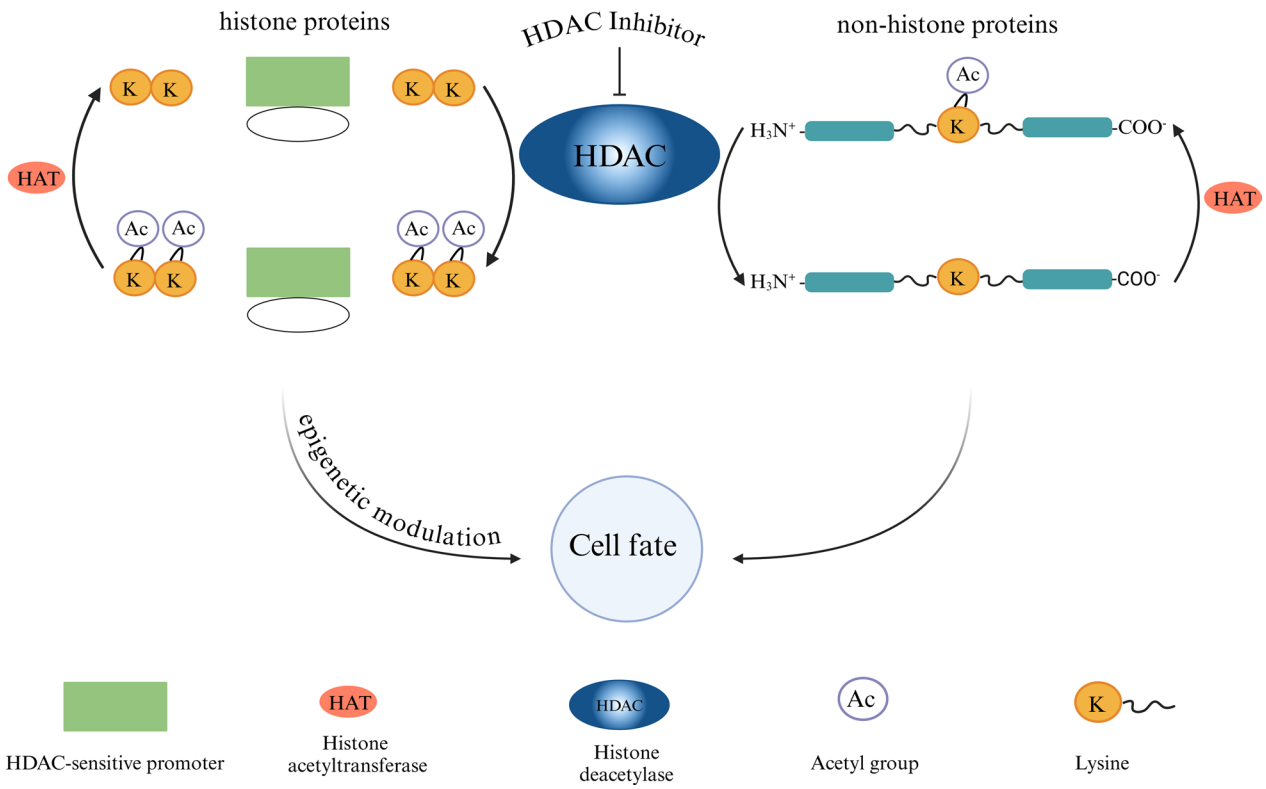

Fig. 2 HDAC inhibitor and its function in HTLV-1 infection (created with biorender). Adapted from Zhang et al. [83]

Histone methyltransferases inhibitors

EZH2 inhibitors

The enhancer of zeste homolog 2 (EZH2)-containing polycomb repressive complex 2 (PRC2) catalyzes the trimethylation of histone H3 at lysine 27 (H3K27me3). This alteration may cause target genes' CpG islands to become methylated, which would silence transcription and possibly aid in the development of cancer. Several malignancies, notably adult T-cell leukemia/lymphoma (ATLL), have poor prognoses and tumor progression associated with elevated EZH2 expression and elevated H3K27me3. EZH2 overexpression and the resulting H3K27 trimethylation may play a critical role in ATLL initiation and progression. Dysregulation of signal transduction pathways contributes to altered EZH2 expression in HTLV-1-driven ATLL carcinogenesis. When EZH2 is inhibited or transcriptionally silenced, H3K27me3 decreases, and tumor suppressor gene expression is restored in HTLV-1-infected T- and ATLL cells. Histone modification and promoter methylation may be essential factors in inactivating tumor suppressor genes, such as NDRG2 [110].

Target genes are transcriptionally repressed when EZH2, a histone methyltransferase and the catalytic member of the polycomb repressive complex 2 (PRC2), trimethylates lysine 27 on histone H3 (H3K27me3) [111, 112]. This epigenetic modulator is crucial for the development, chemoresistance, and carcinogenesis of numerous cancer types [112, 113]. Overexpression of EZH2 and its mutations are related to tumor malignancy for various kinds of cancers [111]; therefore, given its multifaceted properties in cancer, EZH2 has become one of the promising therapeutic targets, and several inhibitors are presently under investigation in various preclinical and clinical studies [113, 114].

EZH2 inhibitors indeed hold promise in several cancer therapies. Tazemetostat (EPZ-6438), GSK2816126, and CPI-1205 have reached clinical trials for hematologic malignancies and solid tumors [115].

Recent studies disclosed EZH2 as a putative target in ATLL. The polycomb repressive complex 2 component EZH2 is involved in the epigenetic reprogramming of ATLL cells, which often leads to the downregulation and silence of tumor suppressors. Pharmacological inhibition has shown great promise in the targeted eradication of HTLV-1-infected and leukemic cells [21]. The EZH2 inhibitor DZNep induces apoptosis in adult T-cell leukemia/lymphoma cells by BCL2 suppression via regulation of Mir-181a [116].

Table 3 Summary of HDAC inhibitors

HDAC inhibitor	Class	Mechanism of action	ATLL effects	Clinical status/trial phase	Adverse effects	References
Vorinostat (SAHA)	hydroxamic acid	Inhibits HDACs I & II; promotes histone acetylation, reactivates tumor suppressor genes, triggers cell cycle arrest, induces apoptosis	Anti-proliferative effects; anti-tumor efficacy	Approved for the treatment of cutaneous T-cell lymphoma (CTCL)	Gastrointestinal symptoms, fatigue, and thrombocytopenia	[88, 88–93]
Romidepsin	A cyclic peptide	Prodrug inhibits HDACs I & II, alters gene expression, and triggers cell cycle arrest, apoptosis, and autophagy, effectively preventing tumor growth and extending the survival of ATLL models	Promising in preclinical studies; moderate response rates in relapsed/refractory ATLL	Received approval to treat CTCL	Nausea, fatigue, thrombocytopenia, granulocytopenia	[94–98]
Belinostat		Decreases NF-κB activity, induces apoptosis, increases Tax protein levels	Enhanced cell death with AZT; reduced apoptosis with IFNα			[99]
Valproic Acid (VPA)		Augments histone acetylation active DNA demethylation; targets multiple HDACs (excluding 6 & 10), leading to the hyperacetylation of histones H3 and H4, upregulates hundreds of genes in a wide variety of cellular pathways, used in combination with AZT and IFNα to show complete molecular responses	Improved survival (chronic subtypes); cytotoxicity via induction of apoptosis and histone hyperacetylation			[100–105]
Entinostat	Benzamide	inhibits HDAC 1 and HDAC 3, demonstrating anti-tumor activity	suppresses the growth of HTLV-1-infected T-cell lines,			[106, 107]
HBI-8000 (tucidinostat)	Benzamide	Inhibits class I HDACs; inhibits tumor growth, modifies immune system, epigenetically alters cell activity	Induces cell cycle arrest and apoptosis in ATLL cell lines and patient samples who are undergoing their first round of treatment or suffer a relapse			[108, 109]

Nowadays, valemetostat is one of the most effective dual inhibitors of EZH1 and EZH2, showing promise as an antitumor agent in lymphomas, mainly diffuse large B-cell lymphoma and ATLL. In Japan, it was authorized in 2022 to treat ATLL that had relapsed or was refractory [117]. Although valemetostat has promise, cytopenias are a common adverse effect that can typically be controlled without stopping medication [118].

Bromodomain and extra terminal inhibitors (BETIs)

Each member of the BET protein family—BRDT, BRD2, BRD3, and BRD4—has an extra-terminal domain at the C-terminal and two bromodomains at the N-terminal [119, 120]. Through their interactions with acetylated histones and transcription factors, activation of transcriptional machinery, and activation of RNA polymerase II, BET proteins control the transcription of genes [120].

In conclusion, preclinical research shows that BET inhibitors, especially JQ1, work by targeting BRD4 to prevent the growth of Tax-positive HTLV-1-infected cells. By interfering with BRD4's association with acetylated RelA, an NF-κB subunit, JQ1 prevents Tax-induced NF-κB activation and carcinogenesis in HTLV-1-infected cells [121]. Cell cycle arrest, diminished S-phase entry, and induction of apoptosis were observed via E2f1 downregulation [122]. It is also noteworthy to mention that the BET inhibitors dislodge the HTLV-I-regulated BATF3/IRF4 transcriptional circuitry, which acts at the heart of the propagation of ATLL, due to the collapse of the HBZ-driven transcriptional program included in MYC expression [123]. These findings identified a therapeutic potential of BET inhibitors in the treatment of ATLL.

Arsenic-based epigenetic therapies

Arsenicals are outdated but virulent and have been applied in the treatment of a wide range of diseases since ancient times. Their luster was lost after the discovery of antibiotics in the 1940s. There has been some revival of the use of medications containing arsenic in the treatment of virus-related cancers. Treatment with arsenic trioxide combined with IFN-α and nucleoside reverse-transcriptase inhibitor (NRTI) gave a superior cytokine gene expression profile in adults with ATLL associated with human T-cell leukemia virus type 1. Further, it altered the patient from initial immunosuppression to a more immunocompetent state. This is likely due to an improved immune response that assists in the elimination of ATLL cells and the control of infections caused by opportunistic pathogens. In clinical studies, there is a possible anti-leukemia effect in patients with poor prognosis of ATLL, which needs further optimization [124].

Challenges and restrictions of epigenetic treatment

Epi-drugs have very bright prospects for cancer treatment, but there are still a lot of obstacles ahead. Driver genes need to be identified versus those that are stimulated; also, potential side effects may limit the widespread application of these genes. Some epi-drugs received FDA approval, but their optimal use and clinical validation remain to be done. Epigenetic modifications may vary with the context and stages of the disease. Clinical trials are often expensive and may take an extended period. Despite all the challenges, targeting epigenetic modifications still has a place in personalized cancer therapy, mainly when used in combination with other approaches. However, key epigenetic alterations are yet to be identified, and the development of effective strategies for targeting these modifications is of utmost importance for further progress [8, 10, 125, 126].

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