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Histone Deacetylase Inhibitors: Current Status in Treatment of Leukemia

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ABSTRACT

Leukemia, one of leading cancer occurs by the acquisition of gene mutations that confer deregulated proliferation and impaired differentiation. Several histone decaetylase inhibitors (HDACi) have exhibited significant protection against the growth of tumor cells in vitro as well as in vivo. Thus it is anticipated that some HDACi could be efficient anti-leukemic drugs. Here, we summarize the current status of different types of HDACi and their clinical role in therapy of different types of leukemia.

Keywords: Leukemia, HDACi, Hydroxamates, Benzamides, Cyclic peptides, Short chain fatty acids.

1. INTRODUCTION

The term leukemia represents a heterogeneous group of diseases described by the malignant clonal proliferation of blood progenitor cells. These cells primarily grow and expand in the bone marrow, and from there distribute to the entire body via the blood circulation. Based on the kinetics of disease onset and course, as well as the differentiation of the malignant clone, leukemia is classified into acute and chronic, and myeloid and lymphocytic, respectively.[1]

Histones are small basic proteins that form nucleosomes leading to the compact structure of chromatin. These histones have long N-terminal extensions that have been known for decades to undergo epigenetic modifications such as acetylation, methylation, phosphorylation as well as ubiquitylation, sumoylation, and ADP-ribosylation. It is suggested that the balance between the actions of histone acetyltransferase (HAT) and histone deacetylases (HDAC) activity leads to a decreased level of acetylation and decreased expression of genes that control growth and development of various cancerous tissues. Discovery of chromatin-modifying enzymes, HDAC made a revolution in the development of a novel class of pharmacologic agents, HDAC inhibitors (HDACi), which are cytostatic agents that inhibit the proliferation of tumor cells in culture and in vivo by inducing cell cycle arrest, differentiation and/or apoptosis. Thus HDACi have emerged as a new class of chemotherapeutic drugs that regulate gene expression.[2,3]

2. CLINICALLY USEFUL HISTONE DEACETYLASE INHIBITORS FOR LEUKEMIA

2.1 Short Chain Fatty Acid Derivatives

These drugs inhibit both class I and IIa HDAC, but usually show low potency due to the inability to make significant contact with the catalytic pocket of HDAC.

2.1.1 Sodium Phenylbutyrate

Sodium phenylbutyrate (PB) is an aromatic fatty acid initially developed for treatment of urea cycle disorders and thalassemia. It is able to induce hyperacetylation of histone proteins in leukemic cells at millimolar concentrations *in vitro*, but its clinical development has been impeded by its short half-life and adversity in achieving millimolar levels *in vivo*.[4,5] In the phase I trial, continuous 7 day infusion of PB was employed (7/28 schedule: 7 days on, 21 days off schedule) in 11patients with MDS (myelodysplastic syndrome) and 16 patients with AML (acute myeloid leukemia) and a dose of 375 mg/kg/day was recognized as the maximally tolerated dose (MTD). Dose limiting toxicities (DLT) were neurological impediments and were reversible within 24–48 h of stopping the infusion.[6,7]

2.1.2 Valproic Acid

Valproic acid (VPA, di-n-propylacetic acid) is a short chain fatty acid used as an antiepileptic and mood stabilizer. VPA has been shown to affect the growth of malignant cells *in vitro*, to prolong the G1 phase of the cell cycle.[8,9] Generally, valproic acid is well tolerated. The reported leading toxicities are neurologic side effects such as dizziness, tremor, sedation, mild gastrointestinal side effects and hematologic toxicity, including pancytopenia and severe bone marrow hypoplasia. Liver failure and teratogenicity with neural-tube defects have been described.[10] VPA is ineffective for the treatment of leukemia when used alone so it is further evaluated for its antileukemia activity in varied combination with cytarabine (Ara-C), etoposide, 5-azacitidine (5-AZA), decitabin, retinoic acid (ATRA).[11-16]

Sodium N-butyrate and phenylacetate are also reported as fatty acid derivatives with HDAC inhibitory activity but having inadequate clinical efficacy and CNS toxicity during clinical trials.[17]

2.2 Cyclic Peptides

2.2.1 Depsipeptide or Romidepsin (FK228)

Despipepdide is a non-epoxyketone-containing bicyclic tetrapeptide isolated from *Chromobacterium violaceum* with antitumor activity in a broad variety of murine and human tumor cell lines both *in vitro* and *in vivo*. It is a pro-drug and the active moiety is a sulfhydryl group acting as the Zn^{2+}-chelator. It is a more selective inhibitor of the class I HDAC, preferentially blocking HDAC 1 and 2 versus HDAC 4 and 6.[18]

Phase I and II studies have established that depsipeptide has a favorable anticancer activity, particularly in patients with CTCL (cutaneous T-Cell Lymphoma) and peripheral T-cell lymphoma. It was given as an IV infusion at a dose of 13 mg/m^2 on days 1, 8, and 15 of a 28 day cycle. Generally, it is well tolerated with favorable toxicity profile. Common side effects include fatigue, nausea, vomiting, transient thrombocytopenia and neutropenia. Several ECG findings have been expressed during the treatment with depsipeptide, including ST and T wave abnormalities, QTc interval prolongation and cardiac arrhythmias. The Maximum Tolerated Dose (MTD) was found to be 17 mg/^{m2} on days 1 and 5 every 21 days.[19-21]

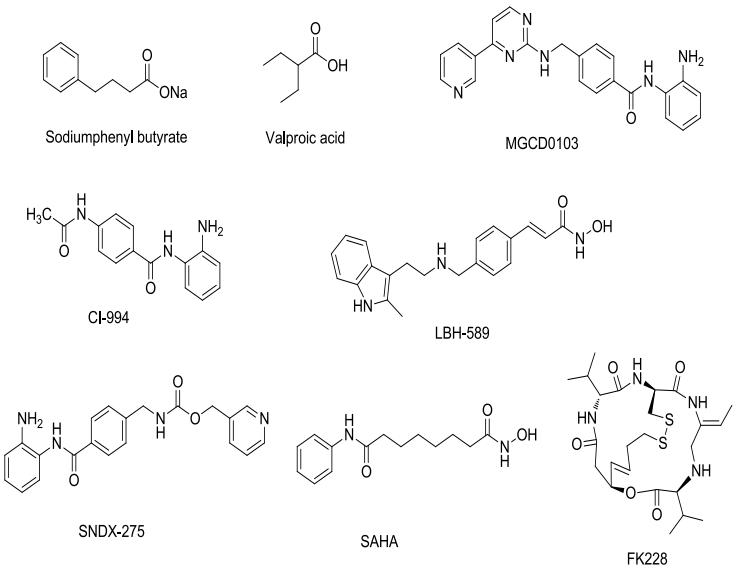

Fig 1: Clinically effective HDACi in leukemia

2.3 Benzamide Derivatives

2.3.1 MS-275 (Entinostat/ SNDX-275)

MS-275 has demonstrated time and dose dependent growth inhibition of leukemia cell lines as well as primary leukemia blasts. It selectively inhibits HDAC 1, 2, and 3.[22]

Phase I clinical trial based on the study of MS-275 in solid tumors, a starting dose of 4 mg/m^2 weekly for 2 or 4 sequential weeks followed by 2-week washout was confirmed.[23] The maximum-tolerated dose was 8mg/m^2 weekly for 4 weeks every 6 weeks and DLT included infections and neurologic toxicity indicating unsteady gait and somnolence. Other frequent non-DLTs were fatigue, anorexia, nausea, vomiting, hypoalbuminemia and hypocalcemia.[24]

2.3.2 MGCD-0103 (Mocetinostat)

MGCD0103 is an isotype specific aminophenylbenzamide and has been shown to inhibit HDAC isotypes 1, 2, 3, and 11.[25] A dose escalation phase 1 study of oral MGCD0103 given three times a week in patients with AML and MDS has been performed. Doses

of MGCD0103 ranged from 20–80mg/m^2 orally. Twenty-nine patients were treated (22 AML, 5 MDS, 1 ALL, 1 CML). Median age was 65 years and 83% of patients had taken previous chemotherapy. Fatigue, nausea, diarrhea, vomiting were the most often reported adverse events. MTD was established at 60 mg/m^2 orally three times a week.[26]

A phase II clinical trial was carried out, starting at a dose of 85 mg/d, three times per week. MGCD0103 exhibited pre-clinical activity against CLL (Chronic lymphocytic leukemia) cells with a LC_{50} (concentration lethal to 50%) of 0.23 micromol/l and increased acetylation of the HDAC class I specific target histone H3. Twenty-one patients received a median of two cycles of MGCD0103 (range, 0-12). Grade 3-4 toxicity consisted of infections, thrombocytopenia, anaemia, diarrhoea and fatigue. HDAC inhibition was observed in six out of nine patients on day 8. Limited activity was observed with single agent MGCD0103 in high risk patients with CLL.[27]

2.3.3 CI-994

N-acetyl-dinaline (CI-994) is an investigational anti-cancer drug which inhibits histone deacetylases. *In vitro*, CI-994 in combination with cytarabine (ara-C), daunorubicin and mitoxantrone, resulted in moderate synergism. *In vivo*, higher dosages of CI-994 induced complete remissions. The combinations of CI-994/daunorubicin and CI-994/mitoxantrone were also active.[28] CI-994 administration, inhibition of both histone deacetylation and cellular proliferation at the G1 to S transition phase of the cell cycle were noticed.[29] Its clinical studies for anti-leukemia activity have not yet been reported so far.

2.4 Hydroxamic Acid Derivatives

2.4.1 LBH589 (Panobinostat)

LBH 589, a potent HDACi is a cinnamic hydroxamic acid analogue which has been shown to induce apoptosis and histone acetylation in acute leukemia cells. LBH 589 effectively induce apoptosis in ATLL-related cell lines and primary ATLL cells.[30] Low nanomolar concentrations (IC_{50}: 5-20 nM) of LBH589 induces cell-cycle arrest, apoptosis and histone (H3K9 and H4K8) hyperacetylation.[31]

Phase I clinical trials shows that 15 patients (13 AML, 1 MDS, 1 ALL) treated with LBH589 at doses ranging from 4.8 to 14.0 mg/m^2 IV daily for 7 days. Reversible QTc prolongation was the dose limiting toxicity. The MTD (maximum tolerated dose) was not established, as 14 mg/m^2 exceeded it and the lower dose cohort of 11.5 mg/m^2 could not be expanded given the concern for QTc prolongation. 27% of patients were also noted to have grade 3–4 hypokalemia, however no relation was noted between QTc prolongation and hypokalemia. Other toxicities included nausea, diarrhea, vomiting, loss of appetite and thrombocytopenia.[32]

2.4.2 Vorinostat (Suberoylanilide hydroxamic acid, SAHA)

It is a hydroxamic acid multi-HDACi that blocks the enzymatic activity of both Class I (HDAC1, -2, and -3) and Class II (HDAC6) HDACs at low nanomolar concentrations (IC_{50} <86 nM) by directly binding to the active site of these enzymes.[33] Vorinostat-induced DNA damage is accompanies by a G2-M arrest and ultimately apoptosis.[34]

A phase I study of single agent vorinostat in patients with advanced leukemia and MDS was conducted for total of 41 patients, were treated (31 AML, 4 CLL, 3 MDS, 2 ALL, 1 CML) with a classical 3 + 3 dose escalation design. The starting dose was 100 mg orally three times daily for 2 weeks with 1 week washout. Twice daily and three times daily regimens were tested. DLTs included fatigue, nausea, vomiting, and diarrhea. The MTD was established as 200mg BID or 250mg TID daily for 14 days every 21 days. Of the 41 patients, 2 patients achieved CR and 2 CRi. Additionally, 7 patients had HI (>50% decrease in blast count). Median number of cycles to response/improvement was 2 (range, 1–8) and median response duration was 6 weeks. Transient acetylation of histone H3 was observed in all patients, regardless of the dose level or response.[35] The two stage phase 2 clinical trial examined in 37 patients for the toxicity and response rate concomitant with two treatment schedules of the HDACi, vorinostat in patients with relapsed acute myeloid leukemia. In both stages a total dose of 8400 mg of vorinostat was delivered in each 21-day cycle of treatment: in arm A the dose regimen was 400 mg daily whereas in arm B the dose regimen was 200 mg three times daily for 14 days followed by 1 week rest. In arm A (n=15), the confirmed full remission rate was 0% (95% CI, 0% to 23%); this arm was closed at the planned interim analysis. In arm B (n=22), the confirmed full remission rate was 4.5% (1 response; 95% CI, 0.4% to 24%), with a duration of response exceeding 398 days. The median time to treatment failure in arm A was 42 days (95% CI, 26 to 57); although a minimum of four cycles of treatment were planned, 11 patients (79%) received no more than two cycles. The median time to treatment failure in arm B was 46 days (95% CI, 20 to 71); 13 patients (59%) received no more than two cycles of treatment.[36]

3. SUMMARY & CONCLUSION

Leukemia is a type of cancer caused by the acquisition of gene mutations that bestow deregulated proliferation, impaired differentiation. The HDAC has been found to interact with many partners through complex molecular mechanism leading to the regulation of gene expression; they have obtained the interest of a huge scientific community. Several HDACi have been confirmed to competently protect against the growth of tumor cells in vitro as

well as in vivo. Now more effective and well tolerated HDACi, including depsipeptide, SAHA, LBH589, PDX101, MS-275, CI-994 and MGCD0103 are in clinical trials alone or in combination with other anticancer agents. Thus it is anticipated that some of the HDACi could be potential effective anti-leukemic drugs.

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