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The efficacy of HDAC inhibitors in neoplasm treatment

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Abstract

Introduction and purpose: Histone Deacetylases (HDACs) are associated with epigenetic regulation of gene expression. They are responsible of adequate action of not only histone proteins, but also crucial cell cycle proteins, such as p53, NF-κB or alpha tubulin. Recent studies have shown the connection between expression of HDAC and carcinogenesis and impact of HDAC inhibitors on cancer therapy. The aim of the study was to review the recent studies on HDAC inhibitors efficiency in the treatment of hematologic neoplasms and solid tumors. It is a study review from 2010 to 2020 using the PubMed database and ClinicalTrials.gov.

Description of state of knowledge: Most studies related to HDAC inhibitors impact in hematological neoplasms, such as multiple myeloma, Hodgkin lymphoma, T-cell lymphomas and acute myeloid leukemia. Among studied agents panobinostat, vorinostat and showed efficacy. Moreover, some HDACi demonstrated effectiveness in solid tumors treatment, foremost vorinostat in breast cancer and entinostat in non-small cell lung lymphoma.
Summary: Including HDAC inhibitors in tumor treatment could be beneficial for patients, especially those with advanced, relapsed or refractory hematologic neoplasm. However, further studies are necessary to confirm their efficacy and to reveal side effects.

Key words: HDAC, inhibitors, cancer, hematology

1. Introduction and purpose

According to the World Health Organization (WHO), the incidence of cancer in 2040 is estimated to be 29,532,994 (currently: 18,078,957) [1]. New therapies are being sought in the fight against cancer. One of the breakthrough methods is immunotherapy, which is now included in treatment standards. However, it is associated with a number of side effects (such as diarrhea, nausea, vomiting, fatigue, itching of the skin, rash, anemia, increase in the level of liver enzymes ASPAT and ALAT), which constitute a certain limitation in its use [2]. Epigenetics investigate the impact of gene expression changes without interfering DNA sequence in cancer therapy, especially in the treatment of immunotherapy-resistant neoplasms. HDACi (histone deacetylase inhibitors) are an example of epigenetic modulators. Due to their anticancer properties, HDACi have been widely studied as an alternative or adjunct to the current cancer therapies [3]. The purpose of this work is to review the recent literature on the use of HDACi in cancer therapies.

Epigenetics is a way of regulating gene expression without directly interfering DNA sequence and involves mechanisms such as histone and non-histone modifications, chromatin remodeling, DNA methylation or RNA regulations [4]. Histone deacetylase (HDAC) enzymes are particularly important since their interaction with lysine residues plays crucial role in chromatin remodeling by ensuring balance in gene expression. Histone deacetylation increases the interaction between positively charged histones and negatively charged DNA, which results in more condensed, transcription-inactive chromatin state. It is also proved that not only histones are substrates for HDAC, but also cell cycle proteins, such as p53, alpha-tubulin, sp1, NF-κB, Ku70, HSP90. Due to new substrates reveal, histone deacetylases are more often referred to simply lysine deacetylases [5,6].

Histone deacetylase inhibitors are divided into five groups: hydroxamates, benzamides, cyclic tetrapeprides, aliphatic short-chain fatty acids and electrophilic ketones, as the most recent discovered group. Those enzymes affect classical HDAC family, specifically for one class (selective HDAC), or as pan-inhibitors they influence all HDAC classes [7]. However, the interest in the class III inhibitors is increasing [8].

To date, five HDAC inhibitors are FDA-approved as novel anticancer agents: romidepsin (FK228) and vorinostat (SAHA) in cutaneous T-cell lymphoma (CTCL), belinostat (PDX-101) and chidamide in peripheral T-cell lymphoma (PTCL) and panobinostat in multiple myeloma [8].

State of knowledge:

There are some researches focusing on the issue how HDAC inhibitors can improve relapsed or relapsed and refractory multiple myeloma (MM) therapy [9]. The authors studied the impact of panobinostat. 768 patients were divided into 2 groups: 387 were treated with panobinostat, bortezomib and dexamethasone and 381 patients were receiving placebo, bortezomib and dexamethasone. The most important advantages in the panobinostat group were: a longer median follow-up (6,47 months in comparison to the 5,59 months in placebo group) and a longer median progression-free survival (11,99 months in the panobinostat group and 8,08 months in the placebo group) [9]. Some similarities were seen in Richardson et al. research among patients with relapsed and refractory MM – an increase in progression-free survival was higher [10]. Benefits of treatment with panobinostat were greatest in patients who received 2 or more than 2 prior regiments including bortezomib and immunomodulatory imide drug – 12,5 in comparison to 4,7 months [10]. The other study touches vorinostat in the treatment of currently progressing multiple myeloma [11]. Patients were divided into 2 groups: 317 of them were in vorinostat group and 320 in placebo group. Median progression free survival (PFS) was higher in the vorinostat group (PFS=7,63 months) compared with placebo group (PFS=6,83 months) [11].

One of studies covers the impact of panobinostat in combination with ifosfamide, carboplatin, etoposide (P-ICE) in relapsed/refractory classical Hodgkin lymphoma [12]. Panobinostat combined with ICE chemotherapy caused better complete response, but an increased myelosuppression was common [12]. Panobinostat was used in patients with Hodgkin lymphoma at risk for relapse after high dose chemotherapy and autologous stem cell transplant [13]. There were lots of adverse events (AEs) compared to placebo group the most common: diarrhea (88,5%/25%), nausea (57,7%/8,3%), vomiting (46,2%/25%), fatigue (34,6%/25%), thrombocytopenia (26,9%/8,3%), oropharyngeal pain (26,9%/0%), headache (23,1%/0%), nasopharyngitis (19,2%/0%) [13].

Quisinostat was tested in the treatment of patients with relapsed or refractory cutaneous T-cell Lymphoma CTCL [14, 15]. Median PFS was 5,1 months and 8 of 26 patients (30,7%) achieved 50 or more reductions in the modified Severity Weighted Assessment Toll (mSWAT) [14]. Panobinostat was used 3 times every week in bexarotene-exposed and bexarotene-na¨ive patients with CTCL who received 2 or more prior systemic therapies. Reductions in mSWAT were observed in 103/139 patients (74,1%) and the median PFS was 17,3% [15]. Another research, which compared the efficacy of vorinostat combined with mogamulizumab in previously treated CTCL, announced that the use of mogamulizumab resulted in the longer PFS compared to vorinostat (7,7 months vs 3,1 months) [16]. The most common AEs in the vorinostat group were: cellulitis (6/186; 3%), sepsis (5/186; 3%), pulmonary embolism (6/186; 3%) and the death for this reason in 2 [16].

There was a study of using azacitidine with or without entinostat in patients with AML [17]. 47 patients participated in the study, they were randomly assigned into two groups. 24 patients received azacitidine alone and 23 received entinostat additionally. CR or PR was observed only in azacitidine group (4 patients in total), while in group receiving entinostat with azacitidine none of the patients showed response [17].

Another study tested valproic acid (VPA) efficacy [18]. 62 patients with AML and 87 patients with MDS were enrolled into two groups. 70 patients received decitabine alone, and 79 patients received valproic acid orally as addition to decitabine therapy. In VPA group 29 (37%) patients showed complete response, and 46 (58%) patients showed overall response, while in decitabine only group there was 22 CR (31%) and 36 OR(51%) patients respectively [18].

The effectiveness of HDAC inhibitors in solid tumors has not been confirmed. However, HDAC inhibitors in combination therapies have a growing high potential for use [19]. There was a research on entinostat in therapy of locally advanced or metastatic, estrogen positive breast cancer [20]. It was a randomized phase II double-blind study that was conducted under placebo control. 130 patients were divided into two groups: 64 patients were given exemestane and entinostat (EE), and 66 patients were given exemestane and placebo (EP). The average PFS was higher in the entinostat group compared to placebo (4.3 months versus 2,3 month). The OR and CBR did not much differ in the EE and EP groups (OR 6,3 % and 4,6%; CBR 28,1% and 25%). Entinostat combined with exemestane was well tolerated and showed efficacy. Another study was focused on vorinostat efficacy [21]. In randomized, phase I, open-label study patients with metastatic breast cancer were divided into two groups: 25 patients were given vorinostat orally daily and intravenously ixabepilone every 3 weeks., and 24 patients received vorinostat daily and ixabepilone every week. There was no significant difference between two groups in ORR and PFS, however patients who received ixabepilone more frequent demonstrate higher level of neuropathy than the other group. Next research, not randomized II phase, open-label study, was also related to vorinostat efficacy [22]. 43 patients were enrolled and received vorinostat combined with tamoxifen once daily. According to RECIST criteria, 8/43 (19%) patients confirmed objective response and 9/43 (21%) patients had stable disease for about 24 weeks. Median PFS was 29 months, TTP was 10,3 months (6-30 months). Moreover, the combination of vorinostat with tamoxifen demonstrated tumor regression or prolonged disease stabilization in 40% of patients.

There was randomized phase II trial, which studied entinostat impact on IIIB/IV stage non-small cell lung cancer [23]. 132 patients were divided into two groups: 67 patients received entinostat combined with erlotinib and 65 patients received erlotinib with placebo. PFS in the entinostat group and placebo group did not differ (18% versus 20% respectively) [23]. Another study presented the results of open-label, randomized, phase I/II study [24]. In second phase 108 patients were randomly assigned to docetaxel or to docetaxel with resminostat group. There was no significant difference in median PFS in docetaxel and docetaxel with resminostat group - 4,2 (2.8-5.7) months versus 4.1 (1.5-5.4) months respectively. Moreover, AEs would appear more often in resminostat group and the most common were leukopenia, anorexia, neurogenic fever and thrombocytopenia [24].

A randomized, double-blind, placebo-controlled phase II / III study was focused on vorinostat efficacy in malignant pleural mesothelioma [25]. 661 patients were divided into two groups: 329 received vorinostat and 332 received placebo. Median OS did not differ much between the groups and for vorinostat it was 30.7 weeks and for placebo 27.1 weeks.

Summary:

HDAC inhibitors do not yet show application in monotherapy, but they were found to be effective supplement to the basic anticancer treatment. HDACis seem to demonstrate higher efficacy in hematological cancers than solid tumors. Unfortunately, most of the studies are non-randomized or involve few patients. To confirm the enzymes impact in neoplasms therapies, more larger-scale trials are needed. However, based on recent studies, there are some evidence for deacetylase inhibitors to be a promising therapeutic approach in hematological cancers and some solid tumors.

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