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Cardiovascular effects of histone deacetylase inhibitors epigenetic therapies: Systematic review of 62 studies and new hypotheses for future research

Gabriele Giacomo Schiattarella [a,b,1], Anna Sannino [a,c,1], Evelina Toscano [a], Fabio Cattaneo [a], Bruno Trimarco [a], Giovanni Esposito [a], Cinzia Perrino [a,*]

[a] Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy
[b] Departments of Internal Medicine (Cardiology), University of Texas Southwestern Medical Center, Dallas, TX, USA
[c] Baylor Heart and Vascular Hospital, Baylor Research Institute, Dallas, TX, USA

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ABSTRACT

Background: Epigenetic regulation by Histone Deacetylases (HDACs) plays an important role in multiple pathophysiological processes, including tumor growth and cardiovascular diseases. HDAC inhibitors (HDACi) have emerged as important therapeutic agents for multiple human cancers, and several randomized clinical trials have been recently undertaken to test their safety and efficacy in cancer patients. Although HDACi have shown beneficial effects in several preclinical models of cardiovascular diseases, concerns have emerged regarding their potential cardiac toxic effects. The present study assessed the extent and possible significance of cardiovascular adverse effects induced by HDACi administration.

Methods and results: Based on the available published clinical trials reporting cardiovascular effects of HDACi therapy in cancer patients, 62 studies for a total patient population of 3268 were included to perform a systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) requirements. A further analysis was conducted to evaluate cardiovascular effects of the different drugs among the HDACi class. Overall, only a minority of studies reported cardiovascular effect of HDACi, and showed mild but frequent cardiovascular side effects after HDACi treatment in cancer patients.

Conclusions: Future studies will be required to better determine the role and the mechanisms underlying cardiovascular effects of HDACi in the context of oncological therapy and beyond.

1. Introduction

Cardiovascular diseases (CVD) and cancer are the leading global causes of death. One of the most rapidly expanding areas of research in both fields is epigenetics, entailing DNA methylation and post-translational modifications (PTMs) of histones modulating gene expression without alterations of the DNA sequence [1]. Acetylation, the most widely studied PTM, is tightly regulated by histone acetyl-transferases (HATs) and de-acetylases (HDACs) [1], and its role has been extensively investigated over the last decades in CVD [2]. HDACs are conventionally classified in four classes (I, II, III and IV) wherein class I, II and IV are "zinc-dependent" enzymes and class III includes a particular subgroup of "nicotinamide adenine dinucleotide (NAD)-dependent" proteins called sirtuins. Reduced gene expression coupled with increased activity of HDACs (mostly class I, II and IV) is a hallmark of different types of cancer, and therefore targeting HDACs is emerging as an important therapeutic option in several malignancies [3]. Compounds acting as HDAC inhibitors (HDACi) [4] have been shown to reduce cell proliferation, promote differentiation and/or apoptosis of cancer cells *in vitro* and *in vivo* [4,5]. The biological and therapeutic outcome of HDAC inhibition is dependent on the specificity of the compound. Since sirtuins are not inhibited by conventional HDACi, the majority of HDACi "class-effects" depend on the inhibition of class I, II and IV HDACs [6]. So far, three HDACi have been approved by the U.S. Food and Drug Administration (FDA) for patients with cutaneous T-cell lymphoma (CTCL): Vorinostat (ZOLINZA™, Merck), Romidepsin (ISTODAX™, Celegene Corporation) and Belinostat (BELEODAQ™, Spectrum Pharmaceuticals, Inc.), and one has been approved for multiple myeloma: Panobinostat (FARYDAK™, Novartis Pharms Corp.). Other molecules, such as Entinostat, also proved their activity as HDACi in pre-clinical and clinical settings [6], but have not yet received the approval by the FDA. The anticonvulsant valproic acid (VPA) has HDAC inhibitory

* Corresponding author at: Division of Cardiology, Dept. of Advanced Biomedical Sciences, Federico II University, Via Pansini 5, 80131 Naples, Italy.
E-mail address: perrino@unina.it (C. Perrino).
[1] G.G.S. and A.S. equally contributed to this work.

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activity, as well, and has been extensively used in combination with more common anti-cancer drugs (*i.e.* cisplatin, epirubicin, doxorubicin).

Although genetic inhibition of specific classes of HDACs has yielded controversial results in terms of cardiac remodeling and function under pathological conditions, global pharmacological HDACs inhibition has shown potential beneficial effects in preclinical models of CVD [7]. However, phase I and II clinical trials of HDACi in cancer have recently raised concerns on potential cardiac toxicity of HDACi, suggesting a potential cardiotoxic effect [8], that has been subsequently re-dimensioned [9]. Given such spare and contrasting evidence, we performed a systematic analysis based on published clinical trials, in order to elucidate the potential detrimental cardiovascular effects of HDACi used in phase I, II and III oncological trials.

2. Methods

2.1. Study selection

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) requirements. PubMed and ISI Web of Science were searched by entering the following terms in the searching algorithm: HDACi or Romidepsin or Valproate or Vorinostat or Belinostat or Panobinostat or Entinostat and cardiac side effect and heart. No temporal limitation was applied. English was set as a language restriction. Two authors (AS and GGS) independently examined the title and abstract of citations. The full texts of potentially eligible trials were obtained, and disagreements were resolved by discussion. To look for additional relevant studies, the full texts and bibliography of all potential articles were also retrieved in detail.

2.2. Eligibility criteria

Studies were included if reporting data on cardiac effects after HDACi administration in patients with solid or hematological neoplasm who received ≥1 prior systemic therapy, and were excluded if any of the following criteria applied: (1) duplicate publication; (2) absence of data on cardiac effects post HDACi treatment; (3) the outcome of interest was not clearly reported or could not be derived from the published results.

2.3. Study endpoints

The primary endpoint was the incidence of ST-depression/T-wave inversion and QTc-prolongation, as previously defined [10]. As secondary endpoint we analyzed the incidence of hypotension, hypertension, sudden death, atrial fibrillation (AF), ventricular and supra-ventricular tachycardia (VT and SVT, respectively) and reduction in left ventricular ejection fraction (LVEF).

According to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, the severity of adverse effects was defined as follow: grade 1 as mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); grade 2 as moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living); grade 3 as severe or medically significant but not immediately life-threatening (hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living); grade 4 as life-threatening consequences (urgent intervention indicated); grade 5 as death related to adverse effects.

3. Results

The initial search identified 808 articles, of which 85 were retrieved for more detailed evaluation, and 62 [6,11–71] trials were finally included in the study (Fig. 1 and Table 1). The included studies examining the different HDACi were divided as follows: 22 studies for Romidepsin [11–32], 14 for Panobinostat [33–46], 14 for Vorinostat [47–60], 7 for Belinostat [61–67], 4 for Valproate [68–71] and 1 for Entinostat [6]. A total of 3268 patients were identified from 62 studies, and were subsequently divided into six HDACi specific groups for subgroup analyses.

Cardiac side effects in the included studies are reported in Fig. 2 and Table 2. The global incidence of cardiac toxic events was 28.6% for all HDACi, with significant variations between the drugs. Among cardiac adverse effects, the most frequent were ST-depression/T-wave inversion, with a global incidence in the HDACi-treated population of 14.5% (473/3268). Remarkably, about one third of patients receiving Romidepsin (239/944; 25.3%) and one fourth of patients receiving Panobinostat (234/1047; 22.3%) experienced a ST-depression/T-wave inversion. A significant prolongation in the corrected QT interval (QTc) was observed in 4.4% (143/3268) of the total population treated with HDACi. This arrhythmic adverse event was observed in patients treated with Valproate (7.1%), Belinostat (12.2%), Vorinostat (3.4%), Panobinostat (4.3%) and Romidepsin (3.3%). Among the secondary outcomes of interest, ventricular tachycardia (VT) showed an incidence of 0.6% (21/3268) in the whole population. However, this effect was observed only in those patients treated with Romidepsin (19/944; 2.0%) or Panobinostat (2/1047; 0.2%). Hypotension was observed in 2.8% (90/3268) of patients treated with HDACi. Among the 3268 patients treated, there were only four cardiovascular deaths: one patient treated with Romidepsin, one patient treated with Vorinostat, one patient treated with Belinostat (fatal myocardial infarction) and one with Panobinostat (fatal myocardial infarction). The grading the severity of cardiac side effects induced by HDACi showed that the greater part of cardiac side effects falls in the first category, 0 to 1, indicating asymptomatic effects, not demanding the interruption of the treatment (Fig. 3). A grade 2 complication, determining the reduction of the administered drug, was found in 5.4% of patients, while only 4.4% of patients needed drug interruption due to a grade 3 to 4 cardiac side effect.

4. Discussion

This systematic review shows that HDACi administration to cancer patients induces mild but frequent cardiac side effects, mainly ECG abnormalities including ST/T abnormalities and QT prolongation. Unfortunately, the real incidence of cardiac side events induced by HDACi is difficult to establish, since the vast majority of clinical trials involving these drugs did not assess or report this information. Future studies will be needed to determine the extent, prognostic significance and mechanisms underlying cardiac effects of HDAC inhibition.

Cancer results from complex relationships between both genetic and epigenetic alterations [72]. In contrast to genetic mutations, epigenetic modifications are potentially reversible, and therefore the development of novel anti-neoplastic treatments aimed at modifying the epigenetic profile of cancer cells represents one of the most active and promising areas of research in cancer [73]. Based on their mechanism of action, HDACs represent excellent targets for cancer treatment. The efficacy of HDACi as anticancer agents has been demonstrated both *in vitro* and *in vivo*. Therapies with Vorinostat and Romidepsin for patients with CTCL represent the most successful anti-cancer clinical application of HDACi [20,48]. Despite these encouraging, HDACi have not shown the same effectiveness in clinical trials involving solid tumors [74]. Indeed, most patients enrolled in these trials showed only partial response to treatment, with a high prevalence of drug-induced side effects, including cardiotoxicity [75]. Therefore, several concerns related to cardiac safety of this class of agents were raised.

Here we performed, for the first time, a systematic review of the literature analyzing the reported cardiovascular effects of HDACi therapy for both hematological and solid tumors, to estimate the rate and magnitude of HDACi-mediated cardiotoxicity. Unfortunately, among the initially selected studies (n = 808), only a minority (n = 62, 7.6%) reported cardiovascular effects. Moreover, registered cardiac side effects were mainly if not almost exclusively related to ECG findings, and