AsiDNA and HDAC inhibitors: a cross-potentiation team working to kill tumor cells

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Short Title: AsiDNA+HDACi: a mechanism-based drug-cooperation

Abstract:

Purpose: while being registered and used in restricted subet of T-cell lymphoma, HDAC inhibitors (HDACi) have shown limited antitumor effect as single agents. Recent studies have shown an effect of HDACi on DNA damage accumulation, rationalizing their combination with DNA repair inhibitors. In the current study, we propose a novel therapeutic strategy, based on drug combination of HDACi with the pan-DNA break repair inhibitor AsiDNA to promote their antitumor activity.

Experimental design: AsiDNA™ is a double stranded DNA molecule (decoy oligo-nucleotide) that mimics double stranded DNA breaks (DSBs) to interfere with DNA repair, redirecting repair enzymes away from sites of tumor DNA damage. Belinostat is a pan-HDACi displaying a better safety profile compared to other HDACi. We characterized the effects of each drug on DNA break accumulation and genetic instability by γH2AX analysis, COMET assay and micronuclei detection. We further studied the antitumor efficacy of the combination of the two drugs. Finally, we assessed the effect of AsiDNA on the occurrence of acquired resistance after long term treatment with belinostat.

Results: Molecular analyses of DNA damage after treatment demonstrate that belinostat paves the way for AsiDNA efficacy by inducing DNA DSBs as measured by γH2AX accumulation and tail moment increase on COMET assay. Moreover, continuous treatment with belinostat induced an increase of basal genetic instability in tumor cells measured by micronuclei accumulation, a prerequisite for AsiDNA antitumor efficacy. On the other hand, AsiDNA enhances the effects of belinostat on histone acetylation, demonstrating a high potentiation of belinostat activity on its targets by AsiDNA. This mechanism-based cross-potentiation between AsiDNA and belinostat results in a high synergistic antitumor efficacy of the combined treatment in different tumor models. This synergistic effect was further confirmed with several HDACi belonging to different classes. Importantly, the combined treatment do not induce any DNA damage increase and/or lethality in non-tumor cells. Finally, repeated treatments allowed the emergence of resistance to belinostat, which is abrogated in presence of AsiDNA, indicating an unlikely tumor escape to this combined therapy.

Conclusion: Altogether these results indicate a cross potentiation between AsiDNA and belinostat, and support the rational to investigate the clinical activity of this novel synergistic combination in different tumor types. As belinostat has obtained FDA conditional approval, and AsiDNA is already tested in a first-in-man clinical trial, a potential exists for a rapid clinical confirmation of the interest of this new combination.