Pharmacodynamic Drug-Drug Interactions Between Oxaliplatin and HDAC Inhibitors in Colorectal Cancer Cell Lines

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Background

Histone deacetylases (HDACs), enzymes that regulate gene expression, have been proposed as regulators for various signaling pathways, including those altered in neurotoxicity and cancer biology [1,2]. HDAC inhibitors (HDACi) are a class of drugs that was recently approved by FDA as a treatment for various malignancies [1,2].

Oxaliplatin (OHP) is one current chemotherapeutic drug used for colorectal cancer treatment. This molecule can cross-link DNA in order to treat the tumor but it can also generate several side effects [3]. One of the side effects of OHP is chemotherapy-induced peripheral neuropathy (CIPN), which affects sensory neurons and influences patient life-quality for weeks, months or years [4].

Aim of the study

The goal of this study is to evaluate the effect of the combination of HDACi and oxaliplatin on a panel of colorectal cancer cell lines. This is a first step to evaluate the efficacy of the combination in cancer cells and whether there are any potential advantages of specific HDACi based on signal transduction.

Methods

Individual drug potencies (IC_{50} values) were estimated using an inhibitory E_{max} model using OriginPro2023b (OriginLab Corporation). The combination drug effects were simulated using Simulux (Lixoft, Monolix suite) and a competitive and non-competitive equation assuming additive drug effects [6,7]. Simulated and experimental data were compared with GraphPad version 8.

Equation A: *competitive formula*
Equation B: *non-competitive formula*

A.

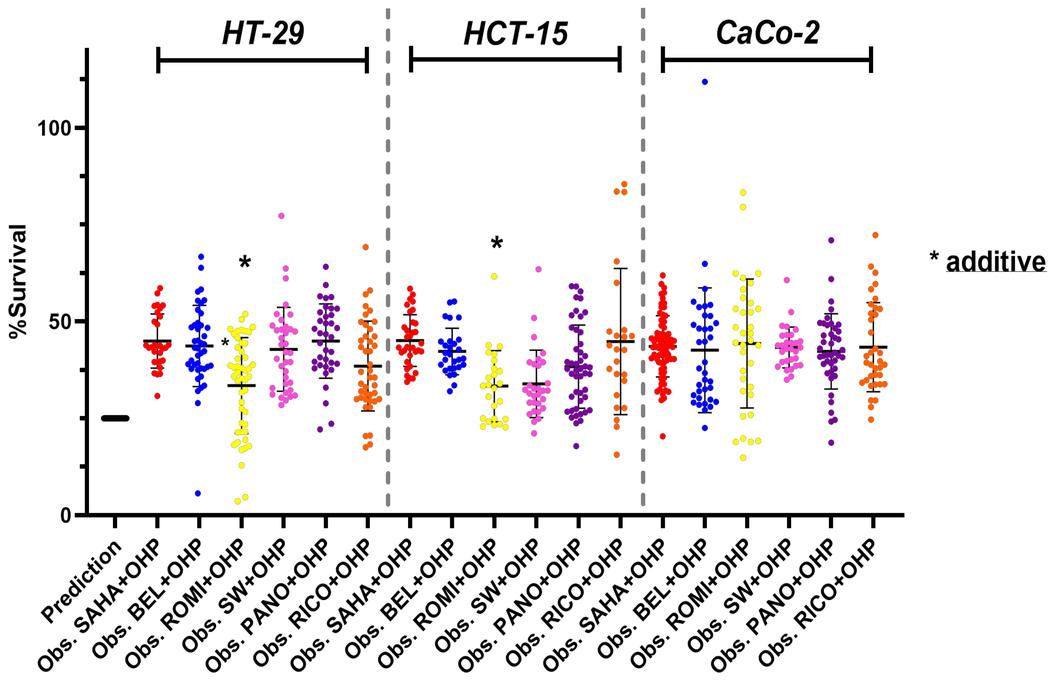
$$E = 100\left(1 - \frac{I_{max_A}(A/(\psi \cdot IC_{50_A}))^{\gamma_A} + I_{max_B}(B\xi/(\psi \cdot IC_{50_A}))^{\gamma_B}}{(A/(\psi \cdot IC_{50_A}))^{\gamma_A} + (B\xi/(\psi \cdot IC_{50_A}))^{\gamma_B} + 1}\right)$$

B.

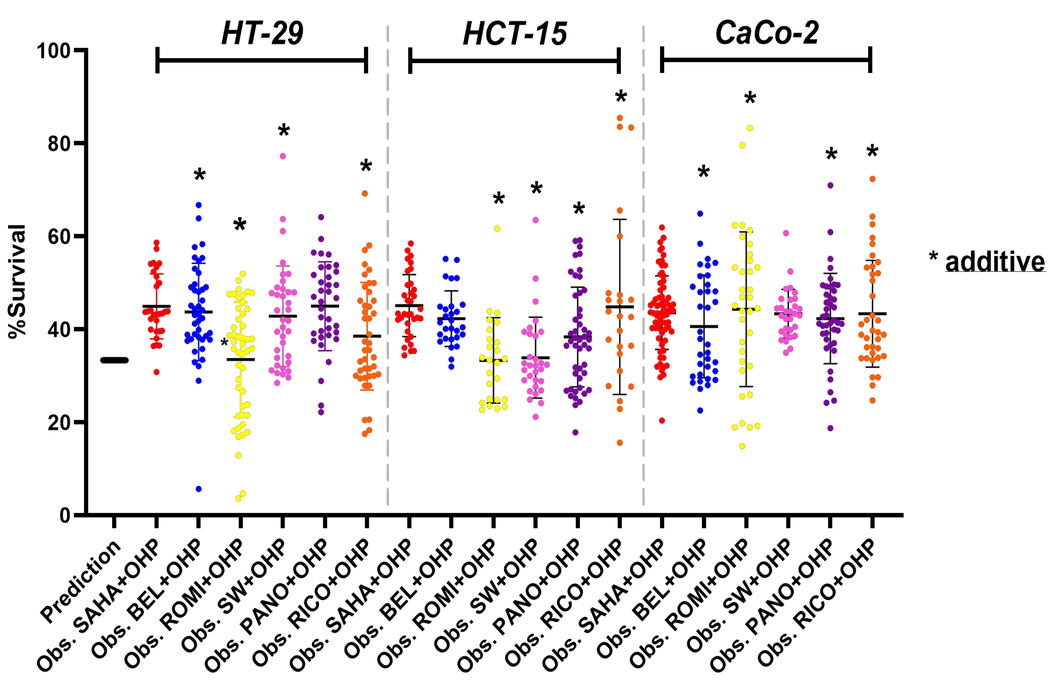
$$E = 100\left(1 - \frac{\left(\frac{I_{max_A} \cdot A^{\gamma_A}}{(\psi \cdot IC_{50_A}))^{\gamma_A}}\right) + \left(\frac{I_{max_B} \cdot (\xi B)^{\gamma_B}}{(\psi \cdot IC_{50_A}))^{\gamma_B}}\right) + (I_{max_A} + I_{max_B} - I_{max_A} \cdot I_{max_B}) \cdot \left(\frac{A^{\gamma_A}}{(\psi \cdot IC_{50_A})^{\gamma_A}}\right) \cdot \left(\frac{(\xi B)^{\gamma_B}}{(\psi \cdot IC_{50_A})^{\gamma_B}}\right)}{\left(\frac{A^{\gamma_A}}{(\psi \cdot IC_{50_A})^{\gamma_A}}\right) + \left(\frac{(\xi B)^{\gamma_B}}{(\psi \cdot IC_{50_A})^{\gamma_B}}\right) + \left(\frac{A^{\gamma_A}}{(\psi \cdot IC_{50_A})^{\gamma_A}}\right) \cdot \left(\frac{(\xi B)^{\gamma_B}}{(\psi \cdot IC_{50_A})^{\gamma_B}}\right) + 1}\right)$$

Results

Non-competitive model



Competitive model



Non-competitive model

Almost all treatments were slightly less than additive. The only exceptions were with *Romidepsin* (ROMI) for HT-29 and HCT-15, which agreed with the prediction of additive effects.

Competitive model

In all cell lines, *Vorinostat* (SAHA) was consistently less then additive while *Romidepsin* (ROMI) was consistently additive in combination with *Oxaliplatin* (OHP). *Belinostat* (BEL) and *Ricolinostat* (RICO) both have an additive effect in CaCo-2 and HT-29 cell lines when in combination with *Oxaliplatin* (OHP).

Conclusions and future directions

The competitive simulation assuming additivity suggests that Romidepsin has a consistent additive effect in all cell lines when in combination with oxaliplatin. In contrast, Vorinostat is consistently less than additive in combination with oxaliplatin in all cell lines. For all other treatments, the response was variable depending on the treatment and cell line.

In the future, a multiplex proteomic assay will be used to evaluate how the combinations affect protein signaling pathways in order to identify potential advantages of specific combinations to minimize neurotoxicity and maximize anti-tumor efficacy.

The modeling of individual drug effects and subsequent simulations assuming additivity were essential to assessing the potential nature of the HDACi and OHP interactions. These preliminary data represent a first step toward assessing the potential mechanisms underlying the combinatorial effects of HDACi and OHP. Future proteomic analyses will be coupled with these results to inform the selection of the most promising drug combinations for future in vivo experiments.

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