Vorinostat, a novel drug against metastasis

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Introduction

On October 6, 2006, the U.S. Food and Drug Administration granted approval to vorinostat (Zolinza), a histone deacetylase inhibitor, for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent, or recurrent disease on or following two systemic therapies.

Interaction with target

Vorinostat binds to the active site of the class I and IIa HDACs, inhibiting its activity.

IC50 < 86 nM

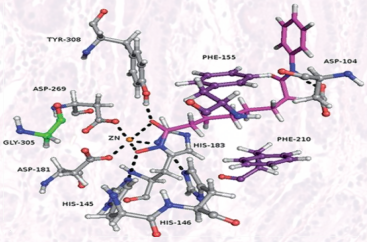


Figure 1. Image of the interactions Between vorinostat and its target. (1)

Adverse effects

Vorinostat presents mild adverse effects:

- diarrhea, vomiting, thrombocytopenia and dehydration.

Epithelial-mesenchymal transition and metastasis

Epithelial phenotype	Mesenchymal phenotype
Tight junctions	Lost of cell junctions
Apical-basal polarity	Change in cell polarity
Type IV and laminin matrix	Cleavage and invasion of basal lamina
Non-migratory	Migration along fibronectin matrix
Express epithelial markers: E-cadherina, occludin	Express mesenchymal markers: N-cadherina, vimentin

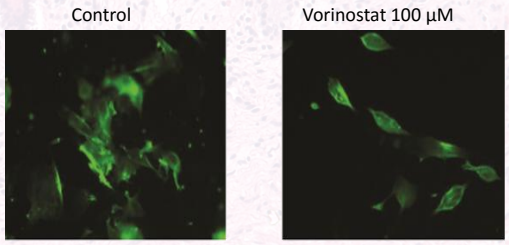
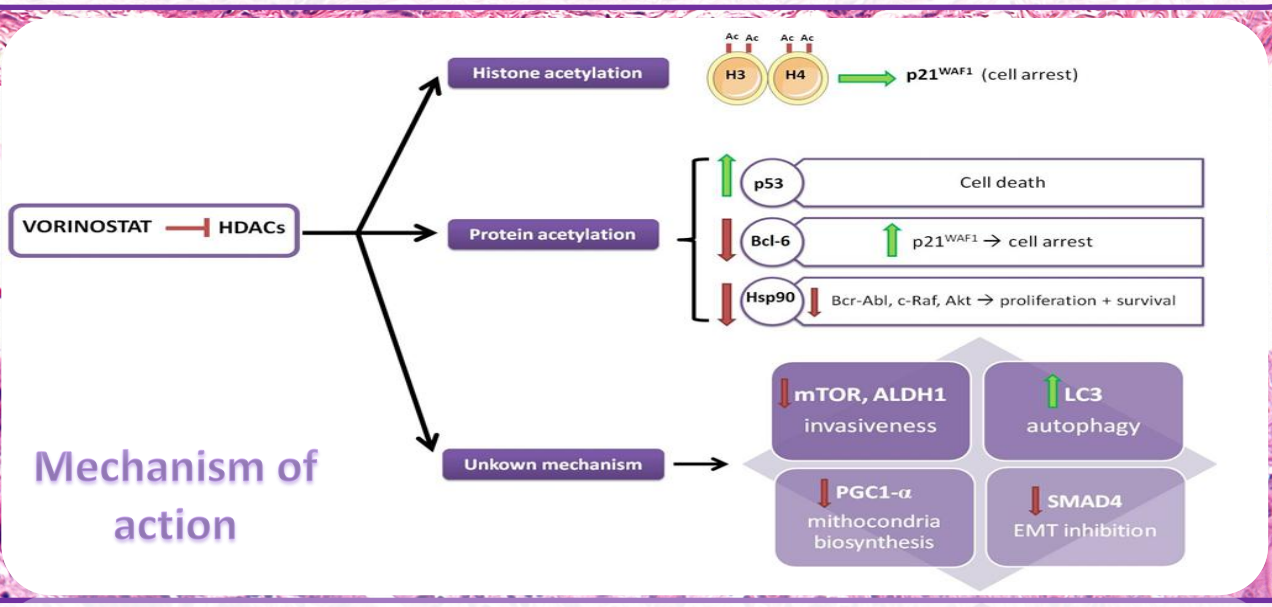


Figure 2. Image of K7M2 tumoral cell line culture with and without vorinostat. (2)



Efficacy

The major trial supporting approval was a single-arm open-label trial that enrolled 74 patients with stage IB and higher CTCL who had failed two systemic therapies. In this study, 30% experienced responses. Vorinostat shows promising effectiveness in combination with other therapies.

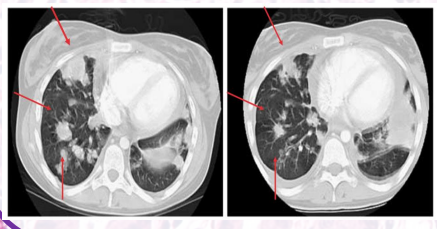


Figure 3. Toracic cavity scanner of a pacient with Hodkin's limphome before and after vorinostat treatment. (3)

Conclusions

- Vorinostat is able to stop the metastasis through the inhibition of HDACs.
- Vorinostat is able to inhibit EMT stopping cancer progression.
- Vorinostat action mechanism is very complex and involves several signalling pathways.
- Vorinostat may be a good candidate as an anticancer drug.

References

1. Pan, D., et al. (2014). Discovery of an orally active subtype-selective HDAC inhibitor, chidamide, as an epigenetic modulator for cancer treatment. *Med. Chem. Commun.*, 5(12), pp.1789-1796.
2. Mu, X., et al. (2015). The HDAC Inhibitor Vorinostat Diminishes the In Vitro Metastatic Behavior of Osteosarcoma Cells. BioMed Research International, 2015, pp.1-6.
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4. Sakamoto, T., et al. (2016). **A Histone Deacetylase Inhibitor Suppresses Epithelial-Mesenchymal Transition and Attenuates Chemoresistance in Biliary Tract Cancer.** PLOS ONE, 11(1), p.e0145985.