Pavlović *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A5.3
http://www.intrinsicactivity.org/2015/3/S2/A5.3
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A5.3

The influence of pretreatment with antioxidants on cytotoxicity of the epigenetic agent vorinostat towards HT-29 colon cancer cells

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Background: Vorinostat is a histone deacetylases (HDAC) inhibitor that promotes apoptosis of malignant cells by several mechanisms. Multiple studies have failed to show an efficacy of vorinostat as a monotherapy against solid tumors, but it has shown a great potential to act synergistically with various chemotherapeutics. Conflicting results were obtained regarding the role of oxidative stress in antitumor effects of HDAC inhibitors, and therefore the aim of our study was to analyze the influence of antioxidants on the cytotoxic activity of vorinostat towards colon cancer cells.

Methods: Human colon adenocarcinoma HT-29 cells were used to assess the cytotoxicity of vorinostat, alone or in combination with the antioxidant agents *N*-acetyl-cysteine (NAC) and α-tocopherol (TOC), using the colorimetric MTT assay. Multiple drug effects were examined by calculating the combination index (CI) using the CompuSyn software: $CI < 1$ is evidence for synergy, whereas $CI > 1$ is evidence of antagonism.

Results: Vorinostat exhibited a modest cytotoxic activity against HT-29 cells, in a concentration-dependent manner. The IC_{50} value of vorinostat was 5.1 μM, while the clinically relevant concentrations are between 1 and 2 μM. In combination studies, HT-29 cells were treated with 1 μM and 2 μM vorinostat, 30 minutes after being treated with 10 mM NAC and 3 μM TOC that displayed negligible antiproliferative effects. Both NAC and TOC managed to sensitize cells towards the activity of vorinostat, especially in a concentration of 2 μM. Calculated CIs of 0.1981 and 0.0803 for NAC, and CIs of 0.3566 and 0.0774 for TOC, in combination with 1 μM and 2 μM vorinostat respectively, suggest their synergistic effects in concentrations that can be achieved *in vivo*. The effect of NAC pretreatment was more pronounced than that of TOC for a lower concentration of vorinostat, while it was similar for a higher concentration of vorinostat.

Discussion: The response to vorinostat may be improved by combining it with antioxidants. The mechanisms responsible for this synergistic effect should be investigated more in-depth.

Acknowledgements: This work is supported by the Ministry of Education, Science and Technological Development of Serbia, grant no. III 41012.

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