The Effect of 5-Aza-2′-Deoxycytidine in Combination to and in Comparison with Vorinostat on DNA Methyltransferases, Histone Deacetylase 1, Glutathione S-Transferase 1 and Suppressor of Cytokine Signaling 1 Genes Expression, Cell Growth Inhibition and Apop

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ABSTRACT

Background: Aberrant methylation and histone deacetylation of tumor suppressor genes (TSGs) are the most epigenetic alterations involving in tumorigenesis. Overexpression of DNA methyltransferases (DNMTs) and histone deacetylase 1 (HDAC1) have been reported in several cancers. The reversion of hypermethylation and deacetylation by epi-drugs such as 5-aza-2′-deoxycytidine (5-AZA-CdR) and vorinostat (SAHA) can restore normal expression of TSGs. Previously, we reported that 5-AZA-CdR and valproic acid (VPA) can inhibit DNMT1 in hepatocellular carcinoma (HCC). The aim of this study was to investigate the effect of 5-AZA-CdR in combination to and in comparison with SAHA on DNMT1, DNMT3a, DNMT3b, histone deacetylase 1 (HDAC1), glutathione S-transferase 1 (GSTP1) and suppressor of cytokine signaling 1 (SOCS1) genes expression, cell growth inhibition and apoptotic induction in hepatocellular LCL-PI 11 cell line.

Materials and Methods: The cells were treated with 5-AZA-CdR and SAHA and then MTT assay, cell apoptosis assay and Real-time quantitative RT-PCR (qRT-PCR) were done.

Results: Both agents indicated significant inhibitory and apoptotic effect ($P< 0.001$). The apoptotic effect of SAHA was more than that of 5-Aza-CdR. The result of qRT-PCR indicated that 5-Aza-CdR decreased DNMT1, DNMT3a, DNMT3b and increased GSTP1and SOCS1 genes expression and SAHA decreased HDAC1 and increased GSTP1 and SOCS1 genes expression significantly. Maximal apoptosis and genes expression were seen with combined treatment.

Conclusion: 5-AZA-CdR and SAHA down-regulated DNMT1, DNMT3a, DNMT3b, and HDAC1 and up-regulated GSTP1 and SOCS1 gene expression by which inhibited cell viability and induced apoptosis, suggesting that they could be used in the treatment of HCC.

Keywords: Epi-drugs; Tumor suppressor genes; Cancer