VARDENAFIL MARKEDLY SUPPRESSES TUMOR GROWTH AND ENHANCES IDARUBICIN-INDUCED ANTITUMOR EFFECTS AGAINST GLIOMA IN VIVO

ASHOUR, A.E.[1,2*], A. ALZAHRANI[2], H. ABDEL-HAMIED[3], K. ZOHEIR[2,4], S. AHMAD[2], S. ALREJAIE[2], A. ABD-ALLAH[2,5]

[1]Basic Medical Sciences Department, Kulliyyah of Medicine, International Islamic University Malaysia.

[2]Pharmacology Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

[3]Pathology Department, College of Medicine for Girls, Al-Azhar University, Cairo, Egypt.

[4]Cell Biology Department, National Research Center, Dokki, Cairo, Egypt.

[5]Pharmacology Department, College of Pharmacy, Al-Azhar University, Cairo, Egypt.

*Corresponding author's email: aeashour@iium.edu.my

Abstract:

Idarubicin (IDA) is highly potent anticancer against glioma *in vitro* but not *in vivo*. Phosphodiesterase (PDE-5) hydrolyses cyclic guanosine monophosphate (cGMP), and is highly expressed in glioma. We proposed that increasing cGMP in the brain by the PDE-5 inhibitor vardenafil (VAR) augments IDA anti-glioma activity. We show that VAR (10 mg/kg) enhanced IDA (0.1mg/kg)-induced tumor growth-inhibitory activity and augmented IDAinduced improvement of survival against rat C6 glioma. Real time PCR results demonstrated that VAR inhibited mRNA expression of PDE-5 in the brains of animals treated with VAR, compared to control-treated group, implicating an important role for the inhibition of PDE-5 in VAR antitumor activity. Animals receiving either VAR alone or VAR+IDA improved survival when compared with control (PBS) or IDA groups. We examined the antiproliferative, pro-apoptotic and anti-invasive activities VAR *in vitro* and showed that VAR inhibited the growth and promoted apoptosis of rat C6 glioma cells. VAR also inhibited the migration and anchorage-independent growth of C6 cell. This suggests that the enhanced antitumor effect of VAR could be due to combined antiproliferative, pro-apoptotic and antiinvasive activities.

Keywords: Idarubicin, vardenafil, glioma, cGMP, apoptosis