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Perifosine enhances bevacizumab-induced apoptosis and therapeutic efficacy by targeting PI3K/AKT pathway in a glioblastoma heterotopic model

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Abstract Bevacizumab (BVZ) as an antiangiogenesis therapy leads to a transient therapeutic efficacy in high-grade glioma. However, the proapoptotic potential of BVZ has not been well elucidated, yet. There is also a tumor resistance to BVZ that is linked to post-treatment metalloproteinases and AKT activities. Herein, the association between therapeutic efficacy and putative proapoptotic activity of low-dose BVZ either alone or in combination with a specific inhibitor of AKT called perifosine (PRF), in a glioma model was investigated. BALB/c mice bearing C6 glioma tumor were treated with BVZ and PRF either alone or combined for 13 days (n = 11/group). At the end of treatments, apoptosis, proliferation and vascular density, in the xenografts (3/group) were detected by TUNEL staining, Ki67 and CD31 markers, respectively. Relative levels of cleaved-caspase3, phospho-AKT (Ser473) and matrix metalloproteinase2 (MMP2) were measured using western blotting. PRF and BVZ separately slowed down tumor growth along with the cell apoptosis induction associated with a profound increase in caspase3 activity through an AKT inhibition-related pathway for PRF but not BVZ. Unlike PRF, BVZ significantly increased the intratumor MMP2 and phospho-AKT (Ser473) levels coupled with the slight antiproliferative and significant antivascular effects. Co-administration of PRF and BVZ versus monotherapies potentiated the proapoptotic effects and reversed the BVZ-induced upregulation of phospho-AKT (Ser473) and MMP2 levels in C6 xenografts, leading to the optimal antiproliferative activity and tumor growth regression and longer survival. In conclusion, BVZ plus PRF renders a paramount proapoptotic effect, leading to a major therapeutic efficacy and might be a new substitute for GBM therapy in the clinic.

Keywords Glioblastoma multiforme · Combination therapy · Bevacizumab · AKT signal · Apoptosis · C6 heterotopic xenograft

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Introduction

Angiogenesis and disrupted apoptosis have been known as hallmarks of malignancy in high-grade glioma called glioblastoma multiforme (GBM) [1]. Angiogenesis is associated with abundant secretion of vascular endothelial growth factor A ($VEGF_A$) by tumor-initiating cells on the endothelial cells (ECs) in a paracrine manner [2, 3]. Among the