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Radiotherapy opens the blood-brain barrier and synergizes with anlotinib in treating glioblastoma

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Abstract

Background: Glioblastoma (GBM) has a poor prognosis and lacks effective treatment. Anlotinib is a multitargeted receptor tyrosine kinase inhibitor (TKI) that may have anti-tumor activity in the central nervous system (CNS). This study aimed to determine the therapeutic value of radiotherapy combined with anlotinib in GBM via preclinical research.

Methods: HPLC-MS/MS was used to assess the concentration of anlotinib in blood and brain samples. Cell proliferation assays, flow cytometry, and colony formation assays were performed in vitro. The potential value of anlotinib or in combination with radiotherapy for GBM treatment was estimated in vivo. Western blotting, immunohistochemistry, and immunofluorescent staining were performed to determine the underlying mechanism.

Results: Anlotinib effectively inactivated the JAK3/STAT3 pathway to inhibit growth and induce apoptosis in malignant glioma cells (MGCs) independent of MGMT expression. Meanwhile, anlotinib induces MGCs G2/M arrest and sensitizes MGCs to radiation. Radiation down-regulates claudin-5 and weakens the blood-brain barrier (BBB), which contributes to the increased distribution of anlotinib in the CNS by 1.0-2.9 times. Anlotinib restrains tumor growth (PCNA), inhibits tumor microvascular proliferation (CD31), and alleviated intratumor hypoxia (HIF 1α) in vivo. Anlotinib alone or in combination with radiation is effective and safe in vivo evaluation.

Conclusions: We discovered that anlotinib, the original small molecule antiangiogenesis TKI, down-regulates JAK3/STAT3 axis with anti-cancer activity alone or in combination with radiation. Anlotinib combined with radiotherapy might be a promising treatment for newly diagnosed GBM in the clinic.

Keywords: Glioblastoma; JAK/STAT3; blood-brain barrier; radiation; tyrosine kinase inhibitors.