Cancer Therapy: Preclinical

Adenovirally Delivered Tumor Necrosis Factor-α Improves the Antiglioma Efficacy of Concomitant Radiation and Temozolomide Therapy

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Purpose: Treatment of malignant glioma involves concomitant temozolomide and ionizing radiation (IR). Nevertheless, overall patient survival remains poor. This study was designed to evaluate if addition of Ad.Egr–tumor necrosis factor (TNF), a replication defective adenovector encoding a cDNA for TNF-α, to temozolomide and IR can improve overall antiglioma effect.

Experimental Design: The efficacy of combination treatment with Ad.Egr-TNF, IR, and temozolomide was assessed in two glioma xenograft models. Animal toxicity and brain histopathology after treatment were also examined. In addition, in an attempt to explain the antitumor interaction between these treatments, the activation status of the transcription factor nuclear factor-κB was examined.
**Results:** Triple therapy (Ad.Egr-TNF, IR, and temozolomide) leads to significantly increased survival in mice bearing glioma xenografts compared with dual treatment. Fifty percent of animals treated with the triple regimen survive for >130 days. Pathologic examination shows that triple therapy leads to a complete response with formation of a collagenous scar. No significant change in myelination pattern is noted after triple therapy, compared with any double treatment. Treatment of intracranial glioma bearing mice with Ad.Egr-TNF and IR leads to cachexia and poor feeding that does not improve, whereas triple therapy results in less toxicity, which improves over 21 days. Both Ad.Egr-TNF and IR activate nuclear factor-κB, and temozolomide inhibits this activity in an inhibitor of κBα (IκBα)–independent manner.

**Conclusion:** This work shows that the addition of adenoviral TNF-α gene delivery to temozolomide and IR significantly improves antglioma efficacy and illustrates a potential new treatment regimen for use in patients with malignant glioma.