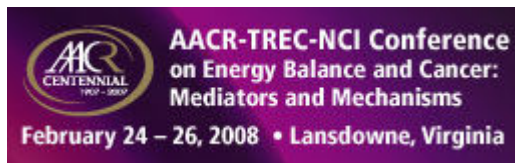


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Cancer Therapy: Preclinical

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 anti-glioma 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 anti-tumor interaction between these treatments, the activation status of the transcription factor nuclear factor- κ B was examined.

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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- κ B, and temozolomide inhibits this activity in an inhibitor of κ B α (I κ B α)–independent manner.

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

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