Epidermal Growth Factor Receptor Antibody-Conjugated Iron-Oxide Nanoparticles: Therapeutic Targeting and Radiosensitivity Enhancement of Glioblastoma

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Introduction

The epidermal growth factor receptor (EGFR) represents the most common alteration present in glioblastoma (GBM) tumors. Iron-oxide nanoparticles (IONPs) conjugated to antibodies specific to the EGFR can be used for magnetic resonance imaging (MRI) contrast enhancement and therapeutic targeting of GBM. We hypothesize that the treatment of experimental GBM with cetuximab-conjugated IONPs can result in radiosensitivity enhancement both in vitro and in vivo after convection-enhanced delivery (CED) in a rodent glioma model.

Methods

Human GBM cells overexpressing the EGFR deletion mutant, EGFRvIII, were treated with control (HBSS; Hanks' solution), free IONPs, cetuximab (a wt EGFR monoclonal antibody that also cross-reacts with EGFRvIII), bioconjugated cetuximab-IONPs and subsequent irradiation (IR; 10 Gy) in vitro. MTT proliferation assay was performed. Immunohistochemical staining was performed to examine the presence of DNA double-strand breaks (DSBs) induced by IR after each treatment (30 min and 4 h). Animal survival studies were performed in 4 different groups of athymic nude mice after implantation of U87MG EGFRvIII cells and treatment with CED of control (HBSS), IONPs, cetuximab, bioconjugated cetuximab-IONPs and subsequent whole brain IR (10 Gy).

Results

Decreased GBM cell survival ***(Figure 1)*** as well as increased formation of DNA DSBs ***(Figure 2)*** was observed in vitro after treatment with bioconjugated cetuximab-IONPs and subsequent IR, compared to other treatment groups. An increase in overall animal survival was found in animals who underwent CED of cetuximab-IONPs and subsequent whole brain IR in comparison to other animal groups ***(Figure 3)***. MRI signal drop was induced by the bioconjugated cetuximab-IONPs ***(Figure 4)***.

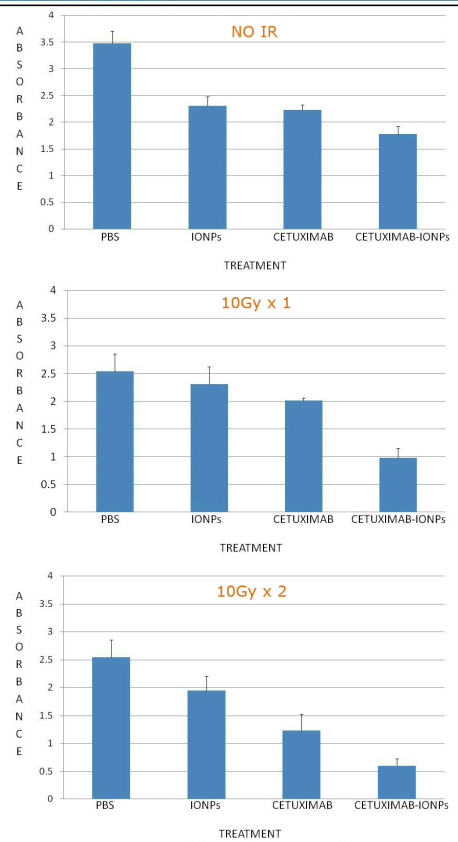

Figure 1: MTT proliferation assay of U87MG EGFRvIII cells. Different treatments were used in combination with IR.

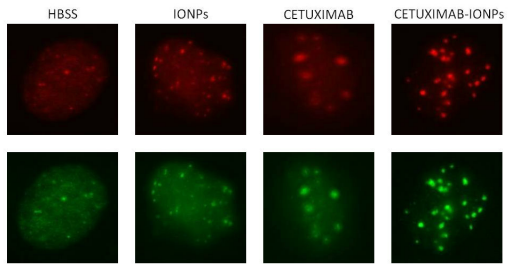

Figure 2: Immunofluorescent staining of U87MG EGFRvIII cells treated with four different treatments and subsequent IR (1Gy). Fixation of cells 4 hours after IR. **RED:** anti-γH2AX **GREEN:** Rhodhamine (anti-53BP1)

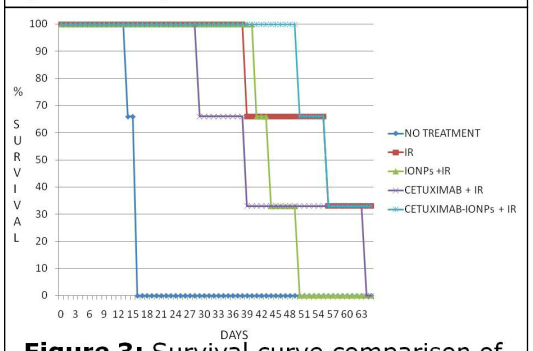

Figure 3: Survival curve comparison of athymic nude mice after intracranial implantation of U87MG EGFRvIII cells and combination treatment by CED of Cetuximab, IONPs, Cetuximab-IONPs and subsequent IR (10Gy x 2), or IR treatment (10Gy x 2), or no treatment (control)

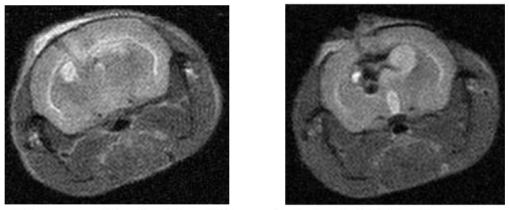

Figure 4: Left: T2-weighted MRI showing a tumor xenograft with bright signal (hyperintense-white area). **Right:** MRI signal drop (hypointense-black area) after CED of Cetuximab-IONPs

Conclusions

IONPs bioconjugated to antibodies specific to the EGFR can provide MRI contrast enhancement of GBM cells and targeted therapy of GBM tumors after CED, as well as radiosensitivity enhancement of GBM tumors. This approach could represent a possible new paradigm for GBM therapy.

Learning Objectives

By the conclusion of this session participants should be able to:

1. Describe the importance of magnetic nanoparticles as a potential multifunctional clinical agent for future cancer therapy.
2. Discuss in small groups the current limitations and the future perspectives of magnetic nanoparticles in malignant gliomas therapy.
3. Identify a potentially effective treatment by using bioconjugated magnetic nanoparticles for targeted therapy as well as MRI contrast enhancement and radiosensitivity enhancement of malignant gliomas.

References

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