Magnetic Drug Targeting: A Novel Treatment for High-grade Intramedullary Spinal Cord Tumors.

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Introduction

High-grade intramedullary spinal cord tumors (IMSCTs) account for 30% of all IMSCTs and carry a poor prognosis. The challenge of IMSCTs is the lack of a clear plane of dissection, making gross total resection hazardous. Radiotherapy has detrimental effects in the spine, especially in children, while chemotherapy exhibits limited penetration and systemic toxicity. In this study, we demonstrate a novel treatment for high-grade IMSCTs using doxorubicin loaded magnetic nanoparticles (MNPs) guided by a magnetic field.

Methods

Athymic rats (Crl:NIH-Foxn1rnu) underwent laminectomy and intramedullary injection of glioblastoma multiforme cells (GBM; 060919) at the midthoracic level, followed by subcutaneous implantation of a 2cm neodymium-iron-boron magnet (0.01 Tesla) at the surgical site. Two weeks after tumor inoculation, 40 µl of doxorubicin loaded MNPs were injected intrathecally at the lumbar level. One week after nanoparticle injection, rats were sacrificed and spinal cord segments were stained and examined for doxorubicin localization. TUNEL assay was utilized to investigate the effectiveness of MNPs to induce apoptosis.

Results

H&E stains revealed tumor growth, with separate Prussian Blue staining demonstrating successful magnetic guidance of nanoparticles to the tumor. Nanoparticles were not detected at other spinal levels. Doxorubicin fluorescence was found to be significantly greater at the tumor site than at other spinal levels ($P<.001$) supporting successful magnetic targeting. TUNEL positive cells were found in the tumor, with evidence of co-localization with doxorubicin, supporting the effectiveness of MNPs to induce apoptosis.

Conclusions

This study demonstrates proof of concept that chemotherapeutic drugs can be successfully delivered to IMSCTs when loaded on MNPs. Advantages of this technique include intrathecal injection, which bypasses the blood-spine barrier, as well as the potential to achieve higher drug concentrations at the tumor site with lower levels of systemic toxicity. Future animal studies and Stage I clinical trials may help further identify the clinical benefit of this new technique.

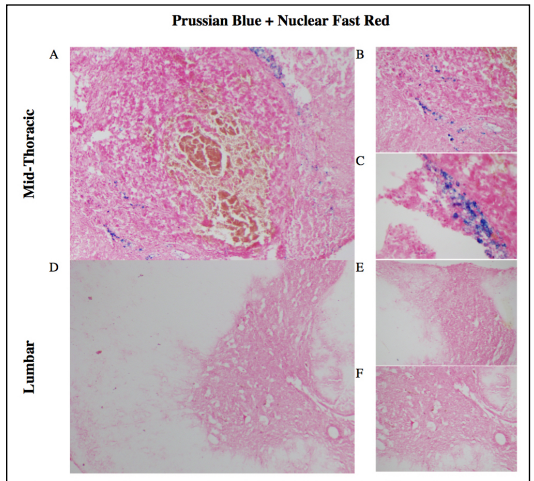

Figure 1: **Prussian blue counterstained with nuclear fast red. A.** MNPs penetrating tumor parenchyma at the mid-thoracic level (100X). **B-C.** Higher magnification of MNPs penetrating tumor parenchyma (200X). **D.** No evidence of MNPs in spinal cord parenchyma at the lumbar level (100X). **E-F.** Higher magnification showing no evidence of MNPs in spinal cord parenchyma at the lumbar level (200X).

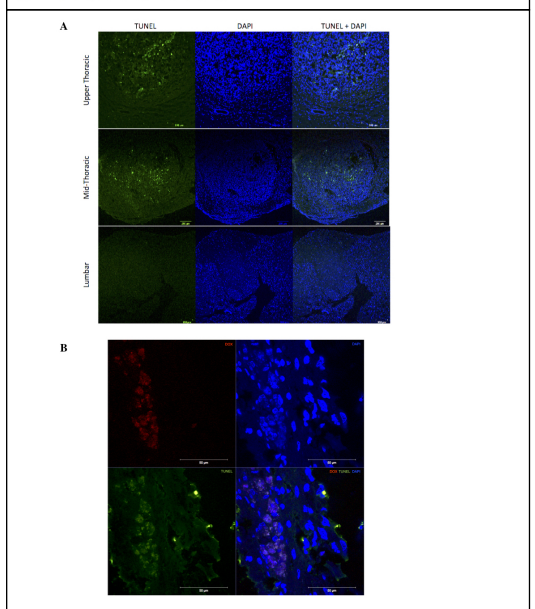

Figure 2: MNP-DOX inducing apoptosis in human GBM 060919 cells *in vivo*. A. TUNEL positive cells (green) were found to be localized in the tumor parenchyma. No evidence of positive TUNEL cells were found at the lumbar level. **B.** Doxorubicin (red) was found to be co-localized with TUNEL positive cells (green) in the tumor parenchyma.

Learning Objectives

By the conclusion of this session, participants should appreciate the need for alternative approaches to high-grade intramedullary spinal cord tumors and recognize the potential benefit of magnetic nanoparticles to localize chemotherapeutic drugs to a tumor site.

References

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2.Samuel N, Tetreault L, Santaguida C, et al. Clinical and pathological outcomes after resection of intramedullary spinal cord tumors: a single