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The application of magnetic nanoparticles for the treatment of brain tumors

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INTRODUCTION

Glioblastoma (GBM), a World Health Organization (WHO) grade IV astrocytoma, is the most common and difficult primary brain tumor to treat (Braun et al., 2012). Even when detected early, the median survival rate for patients is 12–15 months (Adamson et al., 2009; Johnson and O’Neill, 2012). The challenge in treating GBM arises from its resistance to therapies such as radiotherapy and chemotherapy. GBM tumors are quite infiltrative into the surrounding normal brain permitting tumors to recur locally in the majority of patients.

The current standard of care treatment for GBM involves surgery and radiation, with concurrent and adjuvant chemotherapy (Stupp et al., 2005). Surgery permits the bulk of a GBM tumor to be removed in most cases. All patients have residual tumor cells residing away from the resection cavity that eventually lead to local tumor recurrence and the demise of the majority of patients (Hou et al., 2006). The infiltrating GBM cells reside centimeters away from the main tumor mass in normal brain making it difficult for complete surgical removal (Kim et al., 2014). Chemotherapy and radiotherapy of patients after surgery attempts to target these cells to prolong overall patient survival. The blood brain barrier (BBB) represents another challenge to the treatment of GBM tumors by preventing the accumulation of most chemotherapeutics into the brain to target the infiltrative cancer cells (Salazar et al., 1976; Bidros and Vogelbaum, 2009). Surgery and adjuvant therapies pose risks to the patient such as neurologic deficits and systemic toxicities. Known side effects of radiation therapy with chemotherapy for brain tumors include chronic fatigue, nausea, and cognitive deficits (Loehrer et al., 2011).

The BBB remains a formidable challenge in the treatment of GBM and malignant brain tumors. Its selective permeability is due to the presence of specialized endothelial cells, astrocytes, pericytes, and neuronal terminals (Tajes et al., 2014). The semi-permeable membrane that comprises the BBB prevents sufficient exposure of tumors to most chemotherapeutic drugs that are commonly used to fight tumor progression (Liu et al., 2010). Local disruption of the BBB is found within GBM tumors. The tumor vessels in GBM tumors are abnormal both structurally and functionally (Batchelor et al., 2007). The abnormal tumor vessels further impair delivery of therapeutics and create a hypoxic microenvironment that can reduce the effectiveness of radiation and chemotherapy. Antiangiogenic therapy attempts to normalize the tumor vasculature and improve the tumor microenvironment (Jain, 2001, 2005). Outside of the main tumor mass, the BBB is intact where brain cancer cells infiltrate into the surrounding normal brain. The oral chemotherapy agent, temozolomide (Temozodar), can penetrate the BBB and has resulted in prolongation of overall survival patient survival by several months (Stupp et al., 2005).

The challenges associated with the treatment of GBM tumors require novel approaches for a greater impact on patient survival and quality of life for patients.

MAGNETIC NANOPARTICLES (MNPs)

MNPs are most commonly comprised of ferromagnetic iron-oxide (Fe3O4). They are invisible to the naked eye, typically measuring 1–100 nm in diameter (Sandhiya et al., 2009). MNPs can be designed to target cancer by modification of their surface with the addition of a peptide or antibody specific to cancer cells (Hadjipanayis et al., 2010). For biomedical applications, they can deliver targeted therapy to specific regions of the body. MNPs can be administered into the blood stream systemically and directed to a target with application of an external magnetic field (Pankhurst et al., 2003). Particles can be engineered to carry a drug, which can be released once the particles reach their target. In vivo experiments have shown the effects of MNPs within a magnetic field on glioma cells lasting up to 100 min postexposure (Braun et al., 2012). In a separate study with rabbits, intravenous injection of specially designed MNPs and subsequent exposure to an external magnetic field resulted in permanent remission of squamous cell carcinoma tumors (Chertok et al., 2008). While intravenous administration is feasible with tumors in other parts of the body, the BBB remains a formidable challenge for systemic delivery of agents for treatment of brain tumors. For the treatment of patients with GBMs, direct intratumoral delivery provides the...
The localized hyperthermic effect, known as thermotherapy, involves the application of an alternating magnetic field (AMF) which produces heat via the Brownian Néel relaxation process (Thiesen and Jordan, 2008; Deissler et al., 2014).

CONCLUSION
Thermotherapy involving the use of an AMF in conjunction with MNPs has proven to be an effective method for treating patients with GBM. Initial tests have shown that MNPs have minimal toxicities to patients, though further testing must be done to confirm these findings.
FIGURE 1 | Local hyperthermia treatment of a patient with a malignant brain tumor after implantation of MNPs. (A) The patient undergoes an alternating magnetic field (AMF) session (shown in yellow) for generation of local hyperthermia in the region of the tumor. (B) Oscillation of the MNPs (shown in yellow) within and adjacent to the tumor cells provides the therapeutic hyperthermia (thermotherapy) effect. (C) Local implantation of the MNPs within and adjacent to the brain tumor provides a targeted therapeutic effect. (D) Brain tumor cells shown infiltrating normal brain may be more susceptible to the effects of local hyperthermia by greater MNP intracellular uptake and sensitivity to temperature changes.

(Mahmoudi et al., 2012). Much like other methods that are used to combat GBM, MNPs do not serve as a cure on their own; they have shown to be most effective when used as an adjuvant therapy with other treatment modalities. Combining fractionated radiotherapy with thermotherapy has shown a survival advantage in patients with relapsed GBM (Maier-Hauff et al., 2011).

With further research, scientists can bioengineer multitasking MNPs that can be used for imaging, drug delivery, and localized thermotherapy (Hadjipanayis et al., 2013). Better targeting of MNPs may provide more effective treatment of GBM. The bioconjugation of drugs, monoclonal antibodies, or peptides specific to cancer cells will improve targeting. MNPs appear to be well tolerated when delivered directly into the human brain with few side effects associated with them. Further testing of MNPs with standard of care chemotherapy, such as temozolomide, needs to be completed in patients with malignant brain tumors. MNPs will likely assume a larger role in brain cancer treatment, with other adjuvant therapies being used to complement magnetic nanoparticles (Kim et al., 2014).

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REFERENCES
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