Enhancing Glioma Microsurgery With Local Drug and Cell-Based Therapies: Time to Revisit?

Glioblastoma multiforme (GBM) is an aggressive brain tumor that is associated with a limited median survival of 10 to 12 mo.[1,2] Current treatments of GBM involve surgical resection, systemic chemotherapy, and radiation therapy. In spite of that, the progression-free survival is short and inevitably results in high morbidity and mortality.[3] Local delivery of chemotherapeutic or other therapies has long been sought. Carmustine wafers have shown some promise but have been limited by limited efficacy data, and the potential for wound healing issues.[4,5] It has been theorized that the stiffness of the current wafer does not allow for adequate apposition to brain tissue, resulting in its mobilization inside the tumor cavity. It has also been argued that the wafers often get encapsulated by fibrous tissue, which may limit the penetration of carmustine into adjacent brain tissues.

In an effort to establish a novel approach to local drug delivery for GBM, Rowland et al[6] studied a new reservoir medium that is hydrogel based that can potentially be used for intracranial chemotherapy. They reported their results in *Biomaterials*, May 2018.[6] The authors defined four principles that guided the development of their product. First, the vehicle should be softer than brain tissue to prevent mechanically related issues. Second, the material should be malleable and able to fit the resection cavity, but adherent and stiff enough to maintain its configuration. Third, the product's constituents should be tailorable, easily formulated and mixed, since the heterogeneous spectrum of GBM and the variation in physical properties of the medium (i.e. elasticity) might require different formulations. Finally, the materials used should be biodegradable and biocompatible. The authors felt that a hydrogel medium would best fit their criteria.

The hydrogel-based reservoir they used consisted of multiple components essential for the formation of a matrix-like core and ensuring adequate biodegradation and release of the chemotherapeutic agent. The components are cysteine(C)-phenylalanine(F) dipeptides (CF) needed for activation of the degradation pathway in vivo, hyaluronic acid (HA), which provides a medium similar to the brain extracellular matrix, cucurbit[8]uril (CB[8]), which enables cross-linking of the products, the active cargo, and the hydrogel medium. First, HA-CF is chemically produced and is later dissolved in hydrogel under a cell culture media containing antibiotics, growth factors and other chemical agents. It is then stirred for 2 h before CB[8] is added.

In their ex vivo experiment, they added doxorubicin or cisplatin-containing hydrogel reservoir to three cell lines of human glioblastoma specimens and assessed cell viability at 72 h using fluorescent imaging and immunohistochemistry. The results were compared to unprocessed deposited doxorubicin and cisplatin at the same concentrations, the hydrogel reservoir devoid of a chemotherapeutic agent, and no treatment at all. In the three specimens, results were similar. Cell viability was significantly lower in the loaded hydrogel reservoir when compared to the devoid hydrogel reservoir and no treatment. However, in two out three specimens, the cell viability was slightly higher in the loaded reservoir when compared to the chemotherapeutic solutions. In fact, the authors performed a UV spectroscopy drug release study revealed that 8% of the doxorubicin load is released from the hydrogel reservoir within the first 10 h with another slow release over 50 h achieving 11% of the total release. This suggests that total release might take several weeks that could eventually achieve comparable cell viability to nonprocessed chemotherapeutic solutions, without the risk for acute toxicity. Moreover, using fluorescent imaging, the authors were able to confirm at a cellular level, the diffusion of doxorubicin from the hydrogel medium into the surrounding brain tissue. Doxorubicin was seen in the nuclei of cancerous cells 1-h postinjection, delineating 950 micrometers of tissue. Cellular amplification also showed good apposition between both mediums. In terms of toxicity of the hydrogel reservoir, the fluorescent imaging of immunocytochemistry stained glioblastoma cells revealed s similar level of proliferative markers (SOX2 and Nestin) in hydrogel reservoir devoid of chemotherapy and in a nontreated culture. On the other hand, a clear decrease of these factors was observed in chemotherapy-loaded reservoirs. In addition, the authors similarly assessed the levels of inflammatory markers (IL1beta, IL6, and TNFalpha). As expected, loaded hydrogel elicited an upregulation of these markers that is nonapparent in unloaded reservoirs and untreated cell lines. This suggests that the HA-CF, CB[8] hydrogel medium is not toxic by itself.

Rowland et al[6] have successfully presented the physical, cellular, and safety benefits of their hydrogel-based chemotherapeutic reservoir, which may be a promising tool for improving treatment strategies for high-grade gliomas. However, the safety and efficiency of this product needs further research within vivo experimental models and better quantification of presented outcomes—rather than solely relying on fluorescent imaging. Nonetheless, this work will hopefully further stimulate more work on local drug and cell-based therapies for glioma since most recurrences are local and the disease is formally fatal despite decades of research.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Karl R. Abi-Aad, MD[*‡§]
Matthew E. Welz, MS[*‡§]
Devi P. Patra, MBBS[*‡§]
Bernard R. Bendok, MD, MSCI[*‡§¶‖]
[*]*Department of Neurological Surgery*
Mayo Clinic
Phoenix, Arizona
[‡]*Precision Neuro-therapeutics Innovation Lab*
Mayo Clinic
Phoenix, Arizona
[§]*Neurosurgery Simulation and Innovation Lab*
Mayo Clinic
Phoenix, Arizona
[¶]*Department of Otolaryngology*
Mayo Clinic
Phoenix, Arizona
[‖]*Department of Radiology*
Mayo Clinic
Phoenix, Arizona

REFERENCES

1. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro Oncol*. 2016;18(suppl_5):v1-v75.
2. Gaspar LE, Fisher BJ, Macdonald DR, et al. Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Radiat Oncol Biol Phys*. 1992;24(1):55-57.
3. deSouza RM, Shaweis H, Han C, et al. Has the survival of patients with glioblastoma changed over the years? *Br J Cancer*. 2016;114(2):146-150.
4. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol*. 2003;5(2):79-88.
5. Sage W, Guilfoyle M, Luney C, et al. Local alkylating chemotherapy applied immediately after 5-ALA guided resection of glioblastoma does not provide additional benefit. *J Neurooncol*. 2018;136(2):273-280.
6. Rowland MJ, Parkins CC, McAbee JH, et al. An adherent tissue-inspired hydrogel delivery vehicle utilised in primary human glioma models. *Biomaterials*. 2018;179:199-208.