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Local drug delivery for the treatment of brain tumors

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Abstract

The technology of local delivery is being utilized to target multiple pathways for brain tumor therapy. Through the combination of Gliadel, radiation therapy and oral temozolomide (TMZ), median patient survival has increased from 9 to 21 months. To further increase survival, we are exploring the local delivery of TMZ and have shown that in animal models we can achieve 37.5% long term survival. This benefit dramatically increases when combined with radiation therapy. We have also incorporated paclitaxel, a mitotic inhibitor, into a thermosensitive gel depot which provides local delivery, enhances efficacy, and limits systemic toxicity. In combination with TMZ and radiation therapy, this depot significantly increases the long term survivors and improves median survival compared to either therapy alone. This data led to a Phase I clinical trial. Rapamycin, an MTOR inhibitor, anti-angiogenic agent, and anti-proliferative agent has been efficiently incorporated and delivered using biodegradable, controlled release beads which are safe for CNS delivery. These locally delivered beads prolonged survival in the 9L rodent glioma model. Another anti-angiogenic agent, Fc-endostatin, a recombinant human endostatin conjugated to the Fc domain of IgG, showed significantly prolonged survival. Microchip direct delivery to the brain is increasingly attractive. Intracranial microdialysis has determined that the intratumoral concentration of temozolomide was not adversely effected after systemic Avastin dosing, showing that this combination may be helpful to brain tumor patients. This new technique is aiding in our assessment of the interaction between the BBB and compounds given both systemically and locally.

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