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Qunya Ong, Fred H. Hochberg, Michael J. Cima

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Authors
Qunya Ong [a,b], Fred H. Hochberg [c], Michael J. Cima [b,d*]
[a] Harvard-MIT Division of Health Sciences & Technology, Cambridge, MA, USA
[b] The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA
[c] Neurology, Massachusetts General Hospital, Boston, MA, USA
[d] Department of Materials Science & Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

[*] Corresponding author at Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Bldg 76 Room 653G, Cambridge MA 02139, USA. Tel: +1 617-253-6877; Fax: +1 617-258-6936; Email: mjcima@mit.edu

Abstract
Treatment of brain tumor associated edema with systemically delivered dexamethasone, the standard of care, and cediranib, a novel anti-edema agent, are associated with systemic toxicities in brain tumor patients. A tunable, reservoir-based drug delivery device was developed to investigate the effects of delivering dexamethasone and cediranib locally in the brain in an intracranial 9L gliosarcoma rat model. Reproducible, sustained releases of both dexamethasone and solid dispersion of cediranib in polyvinylpyrrolidone (AZD/PVP) from these devices were achieved. The water-soluble AZD/PVP, which exhibited similar bioactivity as cediranib, was developed to enhance the release of cediranib from the device. Local and systemic administration of both dexamethasone and cediranib was equally efficacious in alleviating edema but had no effect on tumor growth. Edema reduction led to modest but significant improvement in survival. Local delivery of dexamethasone prevented dexamethasone-induced weight loss, an adverse effect seen in animals treated with systemic dexamethasone. Local deliveries of dexamethasone and cediranib via these devices used only 2.36% and 0.21% of the systemic doses respectively, but achieved similar efficacy as systemic drug deliveries without the side effects associated with systemic administration. Other therapeutic agents targeting brain tumor can be delivered locally in the brain to provide similar improved treatment outcomes.

1. Introduction

Brain tumor associated edema is a significant cause of morbidity and mortality in patients with malignant brain tumors [1]. It is vasogenic in nature, characterized by the disruption of blood brain barrier (BBB). The exact mechanism behind the breakdown of BBB is unclear. One school of thought is that the tumor production of vascular endothelial growth factor (VEGF) stimulates the formation of gaps in brain endothelium and leads to plasma leakage into the extracellular space of brain parenchyma, resulting in edema [2]. VEGF has been shown to be upregulated in both malignant gliomas [3] and metastatic tumors [4], and its level in high-grade gliomas correlates with the occurrence of edema [5].

Agents that target the VEGF signaling pathway are promising alternatives to corticosteroids, the standard of care for brain tumor associated edema [6]. Cediranib (AZD2171),