Convection Enhanced Delivery of Toca 511 into Recurrent GBM Under Real-Time MR Guidance

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Introduction: Toca 511 (Tocagen, San Diego, CA) is a retroviral replicating vector (RRV) that is presently in Phase 1 trials for treating patients with recurrent glioblastoma (GBM) brain tumors. About 4 weeks after infusion of Toca 511 patients receive courses of oral Toca FC (extended-release 5-fluorocytosine (5-FC)). The vector encodes cytosine deaminase (CD) which converts 5-FC to the anti-neoplastic drug 5-fluorouracil (5-FU). By producing 5-FU locally, this technology has the potential to produce higher intratumoral concentrations of 5-FU than can be attained with systemic administration [1]. Convection enhanced delivery (CED) is a methodology that achieves volumetric tissue coverage via controlled infusions from specifically designed infusion cannulae. CED generates a positive fluid pressure at the cannula tip and convects the infusate in a radial fashion through the extracellular space. CED infusions do not have to cross the blood brain barrier and have been demonstrated to be effective for administering therapeutics in spontaneous glioma in canine models [2]. It can, however, be difficult to predict precisely how CED infusions will evolve, especially in heterogeneous tissue such as GBM. Indeed, suboptimal intratumoral spatial distributions have been proposed as a likely explanation for the poor results of a recent GBM treatment trial [3]. Intraoperative MR imaging offers substantial benefits for administering therapeutics via CED. MR guidance methods, similar to those employed for implanting deep brain stimulators [4], can be used to precisely position the infusion cannula at one or more target locations within a tumor. CED infusions can additionally be monitored with intraoperative MR imaging to assure the desired coverage is being achieved and to take corrective measures when appropriate. We report on an initial group of patients that received Toca 511 via real-time MR-guided CED.

Methods: A total of seven patients with recurrent GBM underwent MR-guided CED infusion of the Toca 511 vector. All patients were consented under a protocol approved by our institutional review committee on human research. Patients were brought to the MR suite and underwent MR imaging to delineate the tumor and select preferred infusion target(s) and cannula tract(s). A burrhole was created at the desired entry site and an MR compatible trajectory guide (ClearPoint, MRI Interventions, Irvine, CA) affixed to the skull. The trajectory guide was oriented under real-time imaging to be directed to the selected infusion site and a 14 or 16-gauge stepped infusion cannula inserted. The vector solution was mixed with an MR contrast agent (Prohance to 1mM final) to enhance CED infused regions and a ramped infusion rate paradigm was employed. At each new cannula location infusion rates began at 1-5µl/min and were ramped up as high as 50µl/min with the larger bore cannula. Continuous T_1-weighted imaging (3D GRE, FOV = 220x172x39mm, isotropic 1mm voxels, TR/TE/flip = 22ms/4.1ms/25^0, BW = 191Hz/pixel, Time = 148sec) was then performed to monitor the infusion. The fractional coverage of the tumor volume and the ratio of the distributed volume (Vd) to infused volume (Vi) were calculated.

Results: The 7 patients had an average GBM volume of 10.5 cm^3 (range=2.6-25.0 cm^3). The desired infusion sites were accurately targeted in all cases and all patients were successfully infused without evidence of reflux along the cannula tract (Figure 1). Infusion progressed until the desired volume was covered or an undesirable infusion pattern developed. Corrections involved either advancing the infusion cannula or re-targeting. The number of infusion sites ranged between 1-4 and 1-2 cannula trajectories were employed. On average, 45% of the tumor volume was covered with the infused therapeutic (range=12-70%) and the mean Vd/Vi ratio was 1.6.

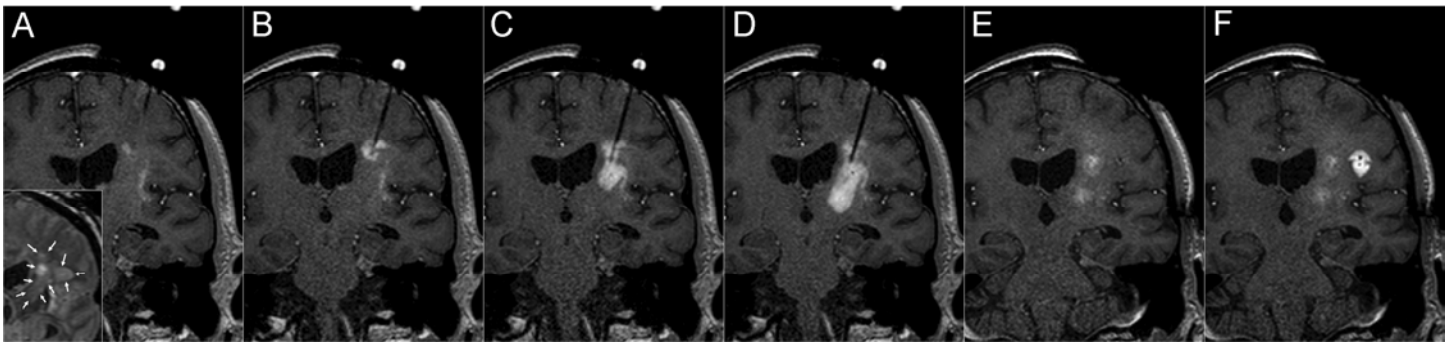

Figure 1: Infusion of a left sided GBM is demonstrated. A baseline image (A) is shown along with an insert outlining the tumor extent (arrows). Three separate infusion sites (B,C,D) are shown along the initial cannula trajectory. The trajectory guide was then re-oriented and a separate more lateral infusion was performed (E:pre-infusion, F: post-infusion). No evidence of reflux along the cannula tract is evident and good coverage was achieved.

Conclusions: Intra-tumoral infusions of an investigational retroviral replicating vector were effectively targeted and monitored with real-time intra-operative MR methods. Intra-operative monitoring allows for correction of the infusion process when the desired coverage is not being achieved. This ability to adapt in real-time enables improved tumor coverage and minimizes the potential for extra-tumoral administration of the vector.

References

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