Radiation Sensitization of Glioma by Locally Delivered Cilengitide in a Rat Brainstem Glioma Model

Sina Tok; Betty Tyler BA; Jeanine Reyes; Momen Sharab; I-Mei Siu PhD; Vanessa Charubhumi; Robert Thomas Wicks BS, BA; Ulrich-Wilhelm Thomale MD; George I. Jallo MD, FACS

Introduction

Clinical trials are assessing efficacy and safety of systemic Cilengitide (CGT) for the treatment of high grade glioma in patients. We have previously shown that CGT delivered locally via osmotic pumps is safe and effectively prolongs survival in a rodent brainstem glioma model. We hypothesize that adding radiotherapy (XRT) to local CGT delivery will be safe and provide an added survival benefit over either therapy alone.

Methods

F344 rats were injected with F98 glioma into the brainstem and were randomized to the following groups on day 5: 1) No therapy (n=8); 2) Local CGT (n=6); 3) XRT (n=8); 4) Low-dose local CGT and XRT (n=7); 5) Local CGT and XRT (n=7). The local delivery system consisted of an osmotic pump containing either CGT (1.6mg) or low-dose CGT (0.8mg) connected to a brain infusion kit and cannula placed in the brainstem at the site of tumor injection. XRT was applied once on day 5 with an external beam single-dose radiation treatment of 20 Gy.

Results

Controls had a median survival of 13 days. The combined XRT and local CGT group showed significantly increased survival ($p<0.01$) with a median survival of 24 Days as compared to the control group. It showed no significant survival benefit ($p=0.31$) over XRT alone (median survival = 18.5 Days).

Conclusions

These results suggest that a combination therapy of intracranial delivery of CGT via convection-enhanced delivery and XRT effectively prolongs survival in a rodent brainstem glioma model but does not seem to provide any survival benefit over XRT alone.

1 Berger MS, Edwards MS, LaMasters D, Davis RL, Wilson CB, Pediatric brain stem tumors: radiographic, pathological, and clinical correlations. Neurosurgery 12: 298-302, 1983

2 Littmann P, Jarret P, Bilaniuk LT, Rorke LB, Zimmermann RA, Bruce DA, Carabell SC, Schut L, Pediatric brain stem gliomas. Cancer 45: 2787-92, 1980

3 Albright AL, Brain stem gliomas. In Youmans J (ed) Neurological surgery. Saunders, Philadelphia, 2603-11, 1996

4 Epstein F, Wishoff JH, Intrinsic brainstem tumors in childhood: surgical indications. J Neurooncol 6: 309-17, 1988

5 Frazier JL, Lee J, Thomale UW, Noggle JC, Cohen KJ, Jallo GI. Treatment of diffuse brainstem gliomas: failed approaches and future strategies. J Neurosurg Pediatr. 2009 Apr;3(4):259-69.

6 Guerin C, Olivi A, Weingart JD, Lawson HC, Brem H, Recent advances in brain tumor therapy: local intracerebral drug delivery polymers. Invest New Drugs 22: 27-37, 2004

Learning Objectives

The reader should learn that locally delivered cilengitide in addition to radiation therapy may be a treatment option for those with glioma, however in this model did not appear more beneficial that XRT alone.

Figure 1

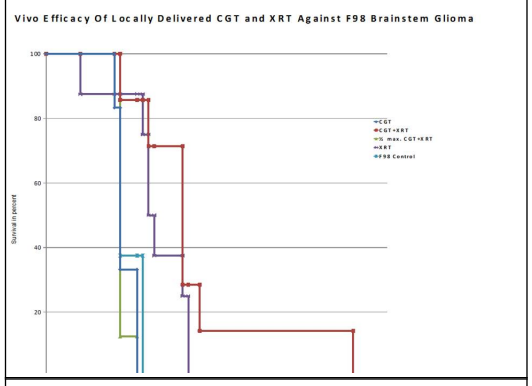

Figure 2

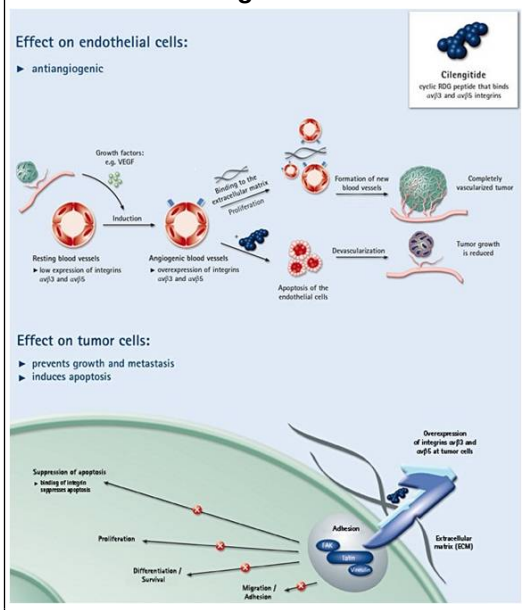

Figure 2. Schematic of Cilengitide pathways. By inhibiting integrins Cilengitide shows anti-angiogenic and anti-invasive activity. © Merck