

## PROGRESS REPORT

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Title of Project: Preclinical Studies on Convection Enhanced Delivery of Carboplatin in Combination with Photon Irradiation for the Treatment of Gliomas

We have continued on with our collaboration with Dr. Helene Elleaume and her co-workers in evaluating the therapeutic efficacy of i.c. delivery of carboplatin by either short-term CED [1] or prolonged i.c. infusions [2] in combination with photon irradiation for the treatment of F98 glioma bearing rats. In our most recent studies, it was shown that 6-day infusions of carboplatin in combination with X-irradiation, yielded the best survival data show (Fig. 1) ever obtained with the F98 glioma model. This tumor has been incurable by all other therapeutic modalities, except for boron neutron capture therapy (BNCT) [3]. ***Supported by funds generously provided by the Grey Ribbon Crusade and the Musella Foundation, studies also have been carried out in my laboratory over the past year.*** Briefly summarized, F98 glioma cells were implanted stereotactically into the brains of syngeneic Fischer rats, and 13 or 17 d. later therapy studies were initiated. Carboplatin (20  $\mu\text{g}/10 \mu\text{L}$ ) was administered by either CED over 30 min (0.33  $\mu\text{L}/\text{min}$ ) or by prolonged infusion using Alzet osmotic pumps (1  $\mu\text{g}/\mu\text{L}/\text{h}$  for 7 d.) beginning at 6 d. following implantation. The estimated tumor volumes were  $\sim 20\text{-}25 \text{ mm}^3$  on d. 13 and  $\sim 60\text{-}80 \text{ mm}^3$  on d. 17. A 15 Gy fractionated dose (5 Gy x 3) of 6 MV photons, delivered by a Siemens linear accelerator (LINAC) was administered beginning on the day following termination of drug administration. Control rats received either carboplatin or X-irradiation alone. Following combination therapy, rats bearing small tumors had a mean survival time (MST) of 83.4 d. following CED and 111.8 d. following pump administration with 40% of the latter surviving  $>180$  d. compared to 55.2 d. for CED and 77.2 d. for Alzet pump delivery of carboplatin alone. In comparison, X-irradiated or untreated control rats had MSTs of 31.8 d. and 24.2 d., respectively. The mean tumor carboplatin concentration following CED (20  $\mu\text{g}/10 \mu\text{L}$ ) was 10.4  $\mu\text{g}/\text{g}$  compared to 1.2  $\mu\text{g}/\text{g}$  in normal brain and 0.3  $\mu\text{g}/\text{g}$  in blood. These studies have demonstrated the superiority of interstitial chemo-radiotherapy compared to monotherapy with either carboplatin or X-irradiation. Animals bearing small tumors had significantly greater MSTs than those with large tumors, and sustained delivery using Alzet pumps was more effective than short term CED. In contrast to these results, only modest increases in MSTs were observed in animals that received either oral or CED of temozolomide plus X-irradiation. ***Although these survival data are the best ever obtained by the Barth lab with the F98 glioma model, there was a significant difference in animals bearing small versus larger tumors. This is the single most important reason why the studies outline in Specific Aim #1 are so important.***

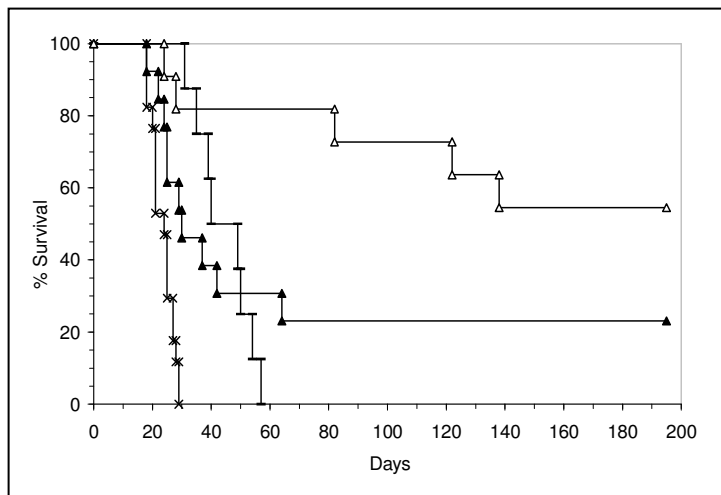


Fig. 1. Kaplan-Meier survival curves for F98 glioma-bearing rats after chemoradiotherapy. Group 5: untreated animals (x); Group 6: X-irradiation only (-); Group 7: carboplatin administered by ALZET™ pump alone (▲), or Group 8: in combination with X-irradiation (△). The survivals of all treatment groups were significantly different from the untreated controls ( $p < 0.0015$ ). The survival of the animals that received carboplatin, followed by X-irradiation was significantly different from irradiated animals ( $p = 0.0014$ ) or those that received carboplatin alone ( $p = 0.0472$ ) (Rousseau J, Barth RF, Moeschberger ML, et al. *Int J Radiat Oncol Biol Physics* 73:530-536, 2009).

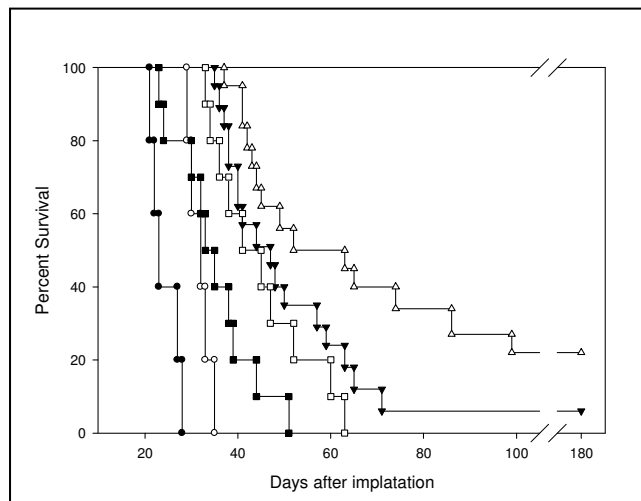


Fig. 2. Kaplan-Meier survival plots of rats F98 glioma bearing either small (~20-25 mm<sup>3</sup>) or large (~60-80 mm<sup>3</sup>) tumors. Survival times in days after implantation have been plotted for untreated controls (●), irradiated rats (○), CED of carboplatin in rats with large tumors (▼), CED of carboplatin + X-irradiation in rats with small tumors (△), CED of carboplatin in rats with large tumors (■), CED of carboplatin + X-irradiation in rats with large tumors (□). Rats bearing large tumors that had received CED of carboplatin + X-irradiation had a MST of 44.9 d, compared to 96.9 d. Rats bearing small tumors that received the same treatment ( $p < 0.01$ ). (Yang, W., Huo, T., Barth, R.F., et al. *Int J. Radiat. Oncol. Bio. & Physics*: to be submitted).

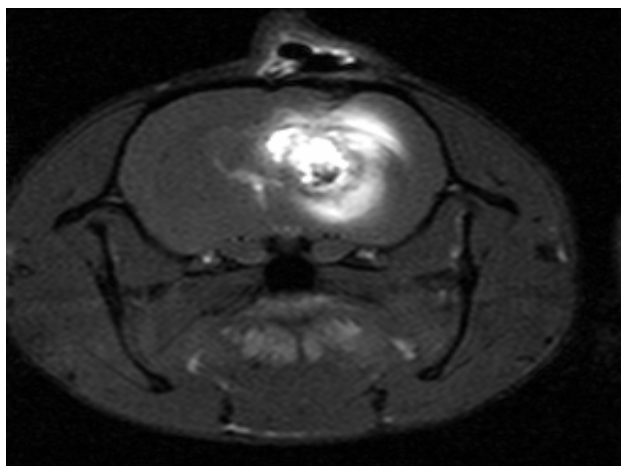


Fig. 3. T1-weighted axial image of an F98 glioma-bearing rat. A mixture of carboplatin (20 µg in 10 µL) and a 1:70 dilution of Gd-DTPA were administered by means of CED over 30 min. Magnetic resonance imaging was carried out 1 hr later. Intense uptake of Gd can be seen in the tumor and in peritumoral white matter indicating efficient dispersion of the mixture by means of CED. (Yang, W., Huo, T., Barth, R.F., et al. *Int J. Radiat. Oncol. Bio. & Physics*: to be submitted)

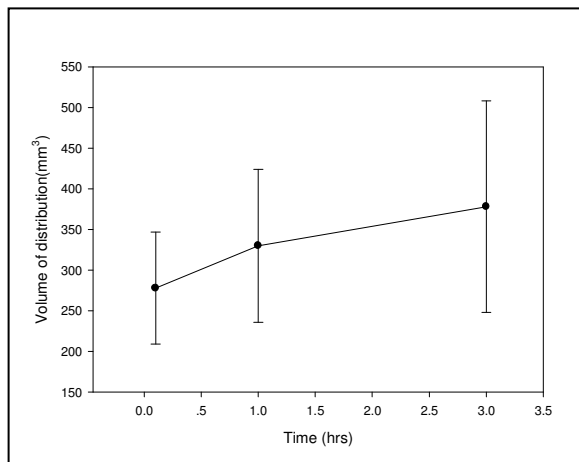


Fig. 4. Volume of distribution ( $V_d$ ) of carboplatin admixed with Gd-DTPA in F98 glioma-bearing rats. Animals received 20 µg of carboplatin in 10 µL, administered by CED over 30 min. Two rats were imaged sequentially beginning immediately following administration and then at 1, 2 and either 3.5 or 4 hrs following termination of CED.  $V_d$  were computed using a program developed by Dr. Ross. Volumes of interest (VOI) were drawn on the T<sub>1</sub>-weighted images, encompassing the entire hyper-intense region (sometimes including hypo-intense region in the center due to gadolinium's susceptibility effect at high concentrations), for quantifying the  $V_d$  of Gd-DTPA in the tissue. There was at least a 5-10 fold increase in the  $V_d$  following CED compared to that following i.t. injection. (Yang, W., Huo, T., Barth, R.F., et al. *Int J. Radiat. Oncol. Bio. & Physics*: to be submitted)

## References

1. Rousseau J, Barth RF, Moeschberger ML, et al.: Efficacy of intracerebral delivery of carboplatin in combination with photon irradiation for treatment of F98 glioma-bearing rats. *Int J Radiat Oncol Biol Phys* 73: 530-536, 2009
2. Rousseau J, Boudou C, Barth RF, et al.: Enhanced survival and cure of F98 glioma-bearing rats following intracerebral delivery of carboplatin in combination with photon irradiation. *Clin Cancer Res* 13: 5195-5201, 2007
3. Barth RF, Yang W, Rotaru JH, et al.: Boron neutron capture therapy of brain tumors: enhanced survival and cure following blood-brain barrier disruption and intracarotid injection of sodium borocaptate and boronophenylalanine. *Int J Radiat Oncol Biol Phys* 47: 209-218, 2000