Assessment of Tumor Perfusion by DSC MRI during Radiation Therapy in Children with Diffuse Intrinsic Pontine Glioma

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Introduction: 20% of all pediatric central nervous system tumors are located in the brainstem and diffuse intrinsic pontine gliomas (DIPG) account for about 80% of these neoplasms [1]. Standard therapy employs fractionated radiotherapy (RT) [2]. Conventional chemotherapy has not demonstrated any survival benefit [1]. Unfortunately, diagnosis is associated with a dismal outcome. Despite many years of research and clinical trials, DIPG is the deadliest brain tumor in children with a median survival time of less than one year, and less than 10% of the patients surviving 2 years after diagnosis [1,3]. Vandetanib (ZACTIMA, AstraZeneca), a potent and selective inhibitor of tumor angiogenesis and tumor cell proliferation, has shown promise in reducing the tumor volume in adult patients with high grade glioma, which is characterized by intense angiogenesis [4]. Our institution conducted a Phase I clinical trial to investigate the maximum tolerated dose (MTD) and efficacy of Vanditanib in combination with standard RT in children with brainstem gliomas. Dynamic susceptibility contrast (DSC) perfusion imaging was performed to investigate a preliminary understanding of vascular proliferation of the tumor during RT. The objective of this study was to study the evolution of perfusion using DSC during treatment of DIPG to provide markers of disease response and progression.

Methods: The protocol is a Phase I study approved by our Institutional Review Board. A total of 35 (15M, 20F, age 3-16y, mean 7y) patients with newly diagnosed diffuse brainstem glioma were recruited to estimate the maximum tolerated dose (MTD) and to determine the dose-limiting toxicity of Vandetanib administered concurrently with radiation therapy (RT). As a Phase I study, escalating doses of Vandetanib were administered to cohorts of three to six patients, and the last 10 patients received the maximum dose level. Vandetanib was administered once per day at the start of RT and continued for up to two years. RT consisted of 1.8 Gy fractions administered 5 days a week for 6 weeks resulting in a total of 54 Gy to the planed target volume. To monitor changes in perfusion after RT, imaging studies were conducted on a 3T scanner (Magneton Trio, Siemens, Germany) at baseline, two weeks, midpoint of RT, and after RT. For DSC, a dynamic series of T_2*-weighted EPI images TE/TR=28ms/1800ms, FOV=210x210mm^2, matrix=128x96, 1562 Hz/voxel, 15 slices, 1.6 x 1.6 x 5.0 mm^3) were acquired during an injection of a paramagnetic contrast agent (Magnevist, Bayer, Montville, NJ, USA). The DSC data was evaluated by selecting a global input arterial input function using the PWI Task Card software (PWI Task Card, MGH, Boston MA, USA). The DSC data, 3D T1 MPRAGE, and 3D T2 SPACE data sets were all coregistered to the same image space using FLIRT (FSL, www.fmrib.ox.ac.uk/fsl). Gray matter and white matter region of interests (ROI) were automatically segmented from the 3D T1 with FAST (FSL). The tumor ROI, defined as hyperintense T2 signal, was then manually segmented from the high resolution T2 weighted images. Tumor perfusion values were measured and normalized to white matter perfusion. Changes in relative tumor perfusion (rCBF) and relative cerebral blood volume (rCBV) before and after RT were tested using the Wilcoxon signed-rank test.

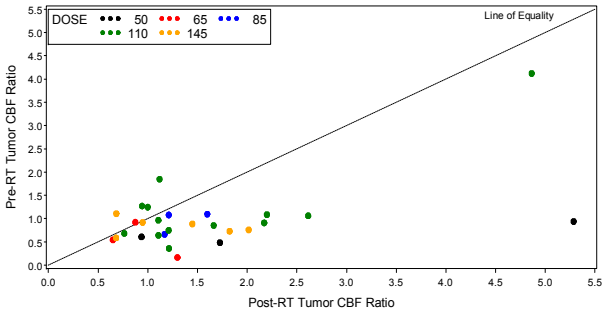

Figure 1 A plot of the change in normalized tumor rCBF before and after radiation therapy (RT). There seems to be a significantly higher rCBF on average post-RT when compared to pre-RT tumor rCBF values (p=0.0002).

Results: Figure 1 is a plot in the change in normalized median tumor rCBF values pre and post RT. There was a significantly higher on average post-RT median tumor rCBF when compared to pre-RT median tumor rCBF (p=0.0002). Figure 2 shows a plot in the change in normalized tumor rCBV before and after RT. Post-RT median tumor rCBV seems to be significantly higher on average compared to pre-RT median tumor rCBV values (p=0.0034). There were no detected increases or decreases on average of rCBF and rCBV values during RT. There was no detected correlation between changes in pre and post-RT in rCBF and rCBV as a function of Vandetanib dose.

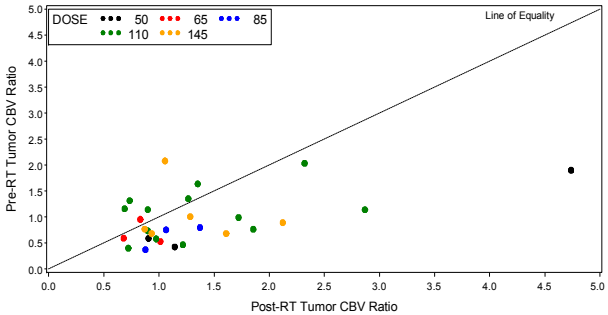

Figure 2 A plot of the change in normalized tumor rCBV before and after radiation therapy (RT). There seems to be a significantly higher rCBV on average post-RT when compared to pre-RT tumor rCBV values (p=0.0034).

Conclusion: DSC was not able to detect changes in rCBF and rCBV related to Vandetanib dose, which could also be attributed to the small number of patients per dose cohort. The increase in post-RT rCBF and rCBV suggest that RT was delivered under favorable conditions. This suggests the tumor had sufficient blood supply to be well oxygenated for increased radio-sensitivity during RT. Future studies will have to stratify tumor rCBF and rCBV with progression free survival to elucidate markers with predictive power.

References: [1] Hargrave D, et.al. Lancet Oncol 2006;7:241-248. [2] Mandell LR, et.al. Int J Radiat Oncol Bio Phys 1999;43:959-964. [3] Broniscer A, et.at. Cancer 2005;103:133-139. [4] Holden SN, et.at. Ann Oncol 2005;16:1391-1397.