Quantification of Therapy Induced Cerebral Blood Flow Changes in Pediatric Diffuse Pontine Gliomas and Normal Appearing Brain Parenchyma by Arterial Spin Labeling during Phase I Combined Radiation and Antiangiogenesis Therapy

Y. Zhang[1], F. H. Laningham[1], R. Loeffler[1], R. Song[1], J. Pfeuffer[2], A. Broniscer[3], Z. Patay[1], and C. M. Hillenbrand[1]

[1]Radiological Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, United States, [2]Siemens Medical Solutions, Erlangen, Germany, [3]Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Introduction

Diffuse pontine glioma is the most devastating, infiltrative neoplasm of the brainstem which accounts for 10% of all CNS malignancies in children and carries a very poor prognosis. This tumor is associated with less than a 10% long-term (5 year) survival rate (1). Despite decades of research, no real survival benefit has been observed despite therapeutic regimens which have utilized various chemotherapeutic and radiotherapy regimens. Local high dose radiotherapy (RT) has been the mainstay of therapy and can postpone tumor progression for only 5-9 months. It is believed that diffuse pontine gliomas, like other high grade glial malignancies of the CNS, can promote their own growth by inducing angiogenesis which increases the vascularity of the tumor. Today, novel therapeutic agents are being designed to inhibit angiogenesis and tumor growth. One such agent, ZD6474 (Zactima), is known to reduce high grade glioma tumor volume by inhibiting proliferation of new tumoral blood vessels and increasing apoptosis. These successes have been observed in clinical trials in treatment of various adult tumors. Some recent studies show that the combination of RT and ZD 6474 has a synergistic effect to treat high-grade gliomas (2). However, ZD6474 has not been used in the treatment of children with cancer. Currently the first clinical trial (Phase I) to employ ZD6474 in the treatment of children with cancer is underway in our institution. It is our goal to assess the anti-angiogenesis effects of this drug, when combined with radiation. We are performing a sequential assessment of brain tissue perfusion at diagnosis, early in therapy, and throughout the duration of follow up. Pulsed arterial spin labeling (PASL) is a promising MRI tool that has the potential of providing serial perfusion measurements of cerebral blood flow (CBF) in the brain. The primary objective of our feasibility study was to determine whether PASL could be successfully used to quantitatively assess cerebral blood flow in brainstem tumors with the ultimate goal to use this technique for non-invasive evaluation of brain tumors receiving conventional (radiation) and novel (antiangiogenetic) therapies. In our study, PASL was applied to pediatric patients with diffuse pontine glioma at sequential time points to evaluate perfusion changes in normal and abnormal (tumoral) brain.

Methods

Subjects: Informed written consent was obtained from the first four patients enrolled in this Phase I study with diffuse pontine glioma (3 to 16 years old, 1 male and 3 females). None of our patients had biopsy or surgery. The diagnosis of diffuse pontine glioma was established using clinical criteria and characteristic MR appearance *MRI*: All the subjects were sedated during MRI scanning. Brain perfusion was measured on a 3T Siemens Trio scanner equipped with an 8-channel (receive-only) phased-array head coil. A PASL sequence (Q2TIPS(3)) was used with the following parameters: TR 2280 ms; TE 23 ms; thickness 5 mm; 20% distance factor; 15 slices and 200 mm FOV. A labeling time (from inversion to saturation) of TI1=700 ms and inflow time (from labeling to start of image acquisition) of TI2=1400 ms were used. A M0 image with long TR and 50 pairs of control and labeling images were acquired for quantitative analysis. Two rounds of measurement were performed, one at the basal ganglia and the other at the level of the pontine tumor to evaluate the perfusion changes in the normal appearing brain parenchyma and in tumor. Brain perfusion was evaluated at three time points: baseline (pre-treatment), at 7 (+ or – 3) days, and at approximately 21 days after initiation of therapy. To co-register CBF maps across multiple time points, a high resolution T2-weighted 3D brain structural image was obtained with the same orientation as the control and labeling images at each time. *Analysis*: Difference images were generated by subtracting the labeling images from the control images after motion correction. Absolute CBF maps were calculated using these difference images. CBF maps were co-registered to the T2 brain structural image acquired at the same time point. Regions of interest (ROIs) were carefully selected by a radiologist to cover several well defined brain regions including the caudate nucleus, lenticular nucleus and thalamus and also brainstem glioma regions (Fig. 1). The same ROIs were applied to the CBF maps along the sequential time points to evaluate brain CBF changes.

Results

Fig. 2 shows the average CBF values across the diffuse pontine glioma patients within each ROI at sequential time points. Compared to the normal appearing brain regions, pontine tumor regions have significantly reduced CBF values, yet PASL seems to be capable of detecting small changes in the tumor over time. Similar CBF tumor values at the second time point were followed by a large decrease of CBF value at the third time point. The right hemisphere shows slightly higher CBF values compared to the left hemisphere. CBF values drop with the positions of selected ROIs moving from the anterior towards the posterior part of the brain. A fairly consistent pattern of perfusion changes with a slightly increase in CBF values at the one week after the start of therapy and then relatively large decrease at the three weeks can be observed in all the ROIs located at the basal ganglia except the left thalamus.

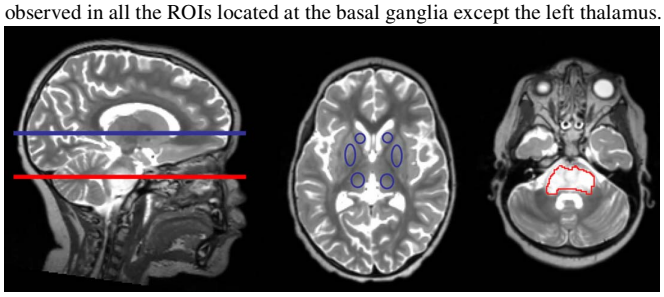

Fig.1 ROIs selected at the basal ganglia and brainstem glioma

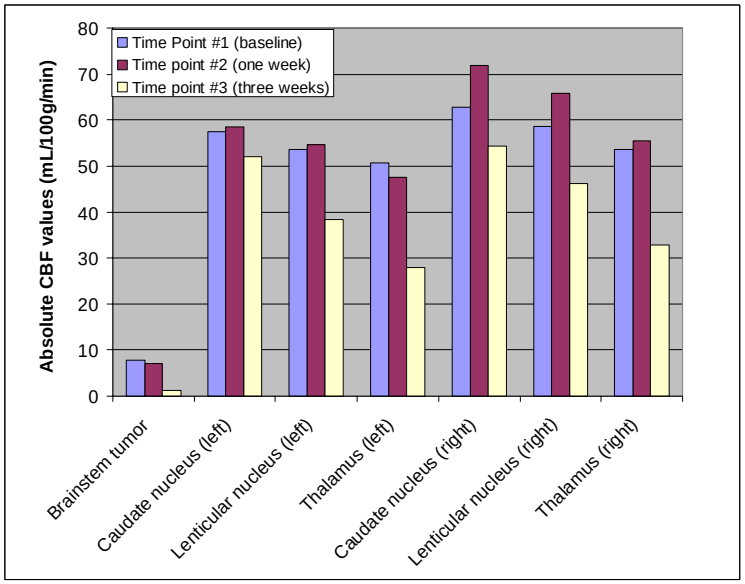

Fig. 2 Mean CBF values across the brainstem patients within the selected ROIs

Discussion

In our limited pilot study PASL seems to have been successful in detecting and quantifying blood flow in both normal brain tissue and brainstem gliomas. This is important because the technique may therefore be used to monitor changes in tumor vasculature induced by conventional radiation therapy or antitumor agents, including antiangiogenetic drugs.

References

(1) Broniscer A and Gajjar A, The Oncologist 9: 197-206, 2004. (2) Damiano V, et al., Clin Cancer Res 11: 5639-5644, 2005. (3) Luh W, et al., Magn Reson Med 41: 1246-1254, 1999.