Evaluation of Treatment Response in Children with Brainstem Glioma by Correlating Cerebral Blood Flow Changes with Combined Vandetanib administration and Local Radiation Therapy

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Introduction

Brainstem gliomas are among the most devastating neoplasms in children and carry a very poor outcome [1]. No treatment benefits have been observed from chemotherapy. Local high dose radiation therapy (RT) can postpone tumor progression for around six months [2]. Vandetanib (ZACTIMA, AstraZeneca), a potent and selective inhibitor of tumor angiogenesis and tumor cell proliferation, has shown the first promise in reducing the tumor volume in adult patients with high grade glioma, which is characterized by intense angiongesis [3-4]. Therefore, the combination of RT and Vandetanib administration may result in a cooperative and long-lasting effect to treat high-grade gliomas compared to each treatment alone [5]. A phase I clinical trial is currently active in our institution for children with diffuse brainstem gliomas. The patients are treated with Vanditanib and local RT. Tumor response to the combined treatment is assessed by volumetric changes but also by functional parameters like microcirculatory tissue perfusion, a potential indicator of vascular changes and re-organization in tumor lesions. Specifically, cerebral blood flow (CBF) is measured in tumor and normal appearing brain parenchyma using a pulsed arterial spin labeling (PASL) technique [6] to avoid intravenous access associated with exogenous tracer techniques. The purpose of this study is to investigate whether CBF can be used as a biomarker to monitor early therapeutic responses to combined Vandetanib administration and local RT in children with brainstem glioma.

Methods

We investigated eight patients enrolled in our IRB approved protocol (age=7.8 ± 4.3 years, 3 males and 5 females). All of them were diagnosed with diffuse brainstem glioma. No patient had biopsy or surgery. All the patients were put into sedation during MR exams. Perfusion data were acquired on 1.5T and 3T scanners by using a Q2TIPS sequence [6] with the following parameters: TR=2280/3500ms for 3/1.5T, respectively, TE=23 ms, slice thickness: 5 mm, FOV: 210 × 210 mm, labeling time TI_1=700ms, inversion time TI_2=1400ms. Two rounds of perfusion measurement were performed at the level of the brainstem and the basal ganglia (Fig. 1, red and blue lines in the left sagittal image) to evaluate changes in tumor and normal appearing brain parenchyma. Perfusion measurement was taken at the end of RT while Vandetanib administration was not interrupted during the course of the therapy. Quantitative CBF maps were calculated following the method described by Wang et al. [7]. Then CBF maps were co-registered to structural T2-weighted images acquired at the same time points. Regions of interest (ROIs) were selected based on the T2-weighted images and then applied to the previously co-registered CBF maps (Fig. 1, right). ROIs of brain parenchyma were picked at the level of the basal ganglia in different radiation dose zones (Fig. 1, T1w images on the left). CBF values in the brain were correlated with radiation doses to investigate the immediate effect of RT on brain perfusion. The overall radiation dose was not different between the patients. To determine the effect of the anti-angiogenesis drug on the tumor, CBF values of the tumor were correlated to the dose of administrated Vandetanib which varied among our patients.

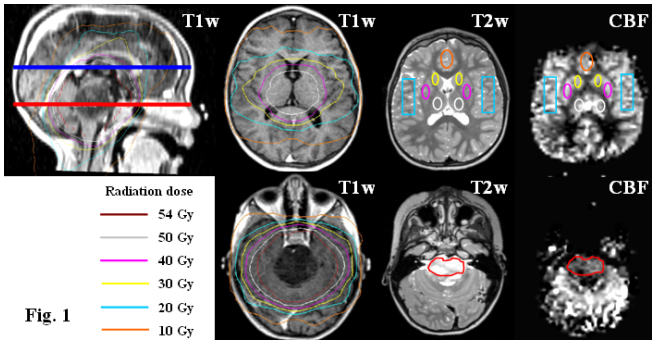


Fig. 1

Results

Fig. 2 shows the measured CBF values as a function of the Vadetanib dose. A negative linear relationship (R = 0.86, p = 0.006) was found. CBF values in the normal appearing brain parenchyma showed high variability at each radiation dose level (Fig. 3). No significant correlation between brain CBF and the radiation dose was revealed (R = 0.27, p = 0.09). But CBF values of regions receiving 30 Gy of radiation and above were marginally lower compared to those from regions with less than 30 Gy of radiation (p = 0.05).

Fig. 2

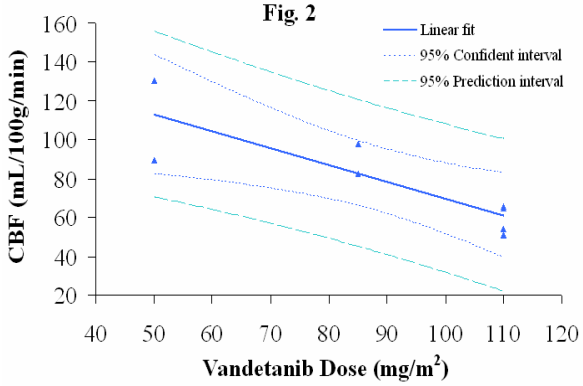
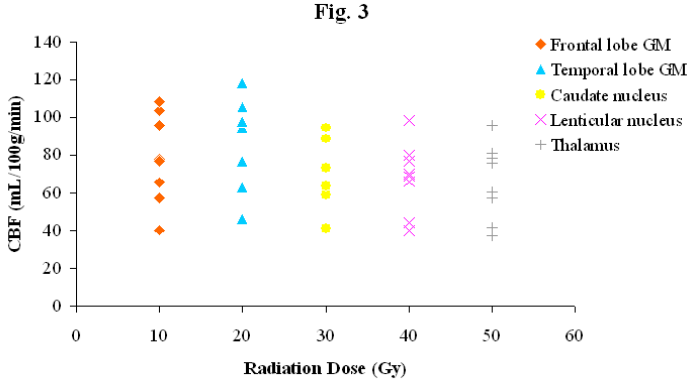


Fig. 3



Discussion and Conclusions

As our results suggest, quantitative CBF measures are able to detect significant differences of tumor perfusion after combined radiation and anti-angiogenic treatment. The negative correlation between tumor perfusion and the Vandetanib dose shows the efficacy of Vadetanib in inhibiting tumor vascularization. Although the correlation between CBF measures in the normal appearing brain parenchyma and the radiation dose is not significant, marginally decreased CBF can be observed in regions receiving 30 Gy of radiation and above, which is consistent with previous studies on radiation toxicity [8]. In summary, CBF seems to be a promising biomarker for monitoring treatment strategies that affect the vascularization of tumor tissue.

References

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