MRI Evaluation of Selective Disruption of the Blood-Brain Barrier by Photochemical Internalization

M. Zhang1, S. J. Madsen1, H. Hirschberg1,2, and H. M. Gach3

1Health Physics, University of Nevada Las Vegas, Las Vegas, Nevada, United States, 2Beckman Laser Institute, University of California Irvine, Irvine, California, United States, 3Research Imaging Facility, Nevada Cancer Institute, Las Vegas, Nevada, United States

Introduction: Failure to eradicate infiltrating glioma cells using conventional treatment regimens results in tumor recurrence and is responsible for the dismal prognosis of patients with glioblastoma multiforme (GBM). Migrating glioma cells are protected by the blood-brain barrier (BBB) that prevents the delivery of most anti-cancer agents. Photochemical internalization (PCI) is being developed to selectively disrupt the BBB since PCI causes the release of membrane-impermeable molecules into the cytosol of target cells [1]. Disruption of the BBB permits access of anti-cancer drugs to effectively target infiltrating tumor cells, and potentially improves the treatment effectiveness for malignant gliomas. BBB disruption was evaluated using MRI after initiating photodynamic therapy (PDT) alone [2] and in combination with PCI in a rat model.

Materials and Methods: PCI treatment, coupling the macromolecule Clostridium perfringens (Cl p) epsilon prototoxin with AlPcS2a-PDT, was performed on non-tumor bearing inbred Fischer rats. An AlPcS2a concentration of 1 mg/kg combined with light fluences of 2.5, 1 or 0.5 J and two Cl p prototoxin delivery methods, intraperitoneal (i.p.) and intracranial (i.c.) were evaluated for the extent of BBB disruption in the group of animals receiving PCI treatment. The control group of animals received an AlPcS2a-PDT only treatment using the same combination of AlPcS2a concentration and light fluences used in PCI.

Treated animals were anesthetized with isoflurane and imaged in a Bruker 7.0 T/20 MRI. T2-weighted MR images (TR: 4200 ms; TE: 36 ms) were acquired to evaluate brain edema, a marker for BBB disruption, induced by PDT-only or PCI treatments. T1-weighted (TR: 700 ms; TE: 14 ms) post-contrast MRIs were acquired 15-20 min after injection of MultiHance (0.8 ml i.p.). Contrast enhancement evident on T1-weighted images was taken as direct evidence of BBB disruption induced by the corresponding treatment. The qualitative analyses of contrast and edema volumes were performed using MIPAV (Medical Image Processing, Analysis & Visualization) software.

Results and Discussion: The PCI effect in rat brain was found to be dependent on light fluence, photosensitizer concentration, Cl p prototoxin concentration and administration route (Fig. 1). Selective disruption of the BBB by PCI was observed for intraperitoneal administration of 1:100 stock dilutions of Cl p prototoxin and photosensitizer concentrations and light fluences of 1 mg/kg and 1 J, respectively (Figs. 1 and 2). Single modality treatments consisting of PDT or Cl p resulted in only minimal damage to the BBB. Both PDT and PCI treatments induced timely, localized BBB disruptions. However, the PCI effect induced a much greater extent of BBB disruption than PDT for a light fluence of 1 J (Figs. 1b and 2). The extent of BBB opening peaked on day 3 and was completely restored by day 18 after PCI. Higher light fluences are required for PDT compared to PCI to achieve similar effects on the BBB. Unfortunately, these higher light fluences increase the potential for edema formation and hence, morbidity and mortality. Therefore, under the appropriate conditions, PCI would appear to be a safe alternative to PDT for selective disruption of the BBB.