Title

SCIDOT-02. A PHASE I STUDY OF CONVECTION-ENHANCED DELIVERY OF LIPOSOMAL-IRINOTECAN (ONIVYDE) USING REAL-TIME IMAGING WITH GADOLINIUM IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMAS: RESULTS THUS FAR

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aim to further validate these findings using a multi-institutional data set. We hypothesize that transfer learning based features when integrated via machine learning may lead to non-invasive determination of *MGMT*pms. METHODS: A total of 270 patients were included across the 3 institutions (Hospital of the University of Pennsylvania (HUP), Jefferson University Hospital (JUH); the TCIA). JUH and TCIA datasets comprised conventional modalities (T1,T2,T2-FLAIR,T1-Gd), whereas HUP dataset had additional modalities (DSC,DTI) as well. We used transfer learning and adapted a convolutional neural network (CNN) model pre-trained on 1.2 million 3-channel images of the ImageNet to extract deep learning features from the given images. A support vector machine multivariately integrated these features towards a non-invasive marker of *MGMTpms*. RESULTS: The cross-validated accuracy of our *MGMT* marker in classifying the mutation status in individual patients was 86.95%, 81.56%, and 82.43%, respectively, in HUP, JUH, and TCIA. Our marker revealed *MGMT*-methylated tumors with lower neovascularization and cell density, when compared with *MGMT*-unmethylated tumors. *MGMT*-unmethylated tumors were found to be more lateralized to the right hemisphere, when compared with *MGMT*-methylated tumors. CONCLUSION: Our findings suggest that transfer learning features when integrated via machine learning allow robust prediction of *MGMTpms* on mpMRI acquired within multiple institutions. The proposed non-invasive *MGMT* marker may contribute to (i) *MGMTpms* determination for patients with inadequate tissue/inoperable tumors, (ii) stratification of patients into clinical trials, (iii) patient selection for targeted therapy, and (iv) personalized treatment planning.

TMOD-41. ORTHOTOPIC PATIENT-DERIVED XENOGRAFT MODELS OF BRAIN METASTASIS: PLATFORMS FOR PRECISION ONCOLOGY AND UNDERSTANDING TUMOR BIOLOGY

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RATIONALE: Brain metastasis (BrM) occurs in 10–20% of cancer patients and results in median survival times of less than 1 year. In order to accurately develop novel treatment strategies, there is an urgent need to establish animal models of BrM that resemble the human disease. OBJECTIVES: We sought to establish orthotopic patient-derived xenografts (PDX) models of BrM from diverse solid cancers to understand biological characteristics of BrM and to test novel drug candidates in their ability to treat BrM. METHODS: 35 PDXs were established by subcutaneous or mammary fat pad implantation and by intracranial injection. PDXs were validated by immunohistochemistry of routine pathological markers in patient specimens and matched primary and intracranial PDXs. PDXs were applied for precision medicine in class II BRAF mutant tumours treated with targeted therapy and in the pre-clinical development of a novel therapeutic agent, DZ-2384, which may have applications in treating BrM. They were also used to understand the underlying biology of leptomeningeal dissemination from parenchymal BrM. RESULTS: PDXs reveal strong similarity to patient specimens by IHC staining. Class II BRAF mutant PDXs are optimally sensitive to BRAF and MEK inhibitors compared to either agent alone. DZ-2384 is effective in slowing the progression of breast cancer BrM. PDXs that most efficiently invade the leptomeninges display loss of E-Cadherin expression, suggesting the role of an epithelial-mesenchymal transition in this process. CONCLUSIONS: PDXs of BrM represent important models that can be employed to test novel therapeutics and to improve understanding of molecular mechanisms engaged by BrM.

TMOD-42. PROSPECTIVE VALIDATION OF AN EX VIVO 3D ASSAY FOR PREDICTION OF TEMOZOLOMIDE RESPONSE IN GLIOBLASTOMA

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Standard treatment for newly diagnosed glioblastoma (GBM) is surgical resection followed by radiation with concurrent temozolomide (TMZ). For those who do not respond there are few clinical options, survival is low, and there no biomarkers to direct the decision of second-line treatment. We have developed a 3D cell culture assay to predict response to TMZ and 11 other potential therapies for GBM. Our assay uses GBM tissue obtained at surgical resection and the test's 7-day turnaround maximizes clinical actionability of results. We performed a small, prospective study examining the ability of the assay to predict response to TMZ. Ten newly diagnosed GBM patients were enrolled over 12 months. Two patients were removed due to refusal of treatment, and three failed the assay (3/8, 62.5% success). The remaining five patients received radiation and concurrent TMZ following surgical resection. Using progression-free survival (PFS) measured from the completion of radiation therapy and setting 4 months as the cutoff for response, we were able to determine the ability of our assay to predict TMZ response. The assay correctly predicted all five patients (100%). The average PFS for the two predicted responders was 8 months compared to the three predicted non-responders at 3 months, p = 0.0634. In this limited dataset, MGMT methylation did not appear to play a role as two of three predicted non-responders were methylated along with one of two predicted responders. Average overall survival of the predicted TMZ responders was 13 months compared to 6 months for the predicted non-responders, p = 0.0634. This early data indicates the potential for this assay to inform clinicians of the best course of action for their patients. Further enrollment of patients into the 3D-PREDICT clinical trial will provide a larger dataset for better validation of the predictive value of this new assay.

ABSTRACTS FROM THE 3RD SNO-SCIDOT JOINT CONFERENCE ON THERAPEUTIC DELIVERY TO THE CNS

SCIDOT-01. NANOPARTICLE DELIVERY OF MIRNAS TO INHIBIT GBM STEM CELLS

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Options for treating high-grade brain tumors remain limited. Recent developments in nanomedicine provide new and exciting opportunities to treat and manage brain tumors. Epigenetic modifications, involving deregulation of non-coding RNAs, in particular miRNAs, are emerging as critical determinants of gene expression and essential drivers of neoplastic phenotypes. Cationic polymers are a class of biomaterials with great promise for targeted molecular therapeutics. We combined this cutting-edge technology with our newly discovered stem cell inhibiting miRNAs to develop nano/miR to treat gliomas. We show these nano/miR distribute throughout an established tumor *in vivo,* and more importantly, delivering these tumor-suppressing miRNAs using PBAE polymers inhibits the growth of established GBM tumor in mouse models. Our findings demonstrate that identifying and validating stem cell-inhibitory in combination with current advances in nanomedicine will undoubtedly impact the development of novel therapies for targeting the CSC population and treating GBM.

SCIDOT-02. A PHASE I STUDY OF CONVECTION-ENHANCED DELIVERY OF LIPOSOMAL-IRINOTECAN (ONIVYDE) USING REAL-TIME IMAGING WITH GADOLINIUM IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMAS: RESULTS THUS FAR

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BACKGROUND: Chemotherapy for high grade gliomas (HGG) is limited by the blood-brain-barrier (BBB). Convection enhanced delivery (CED) improves chemotherapy delivery by utilizing fluid convection obviating the challenges of crossing the BBB while minimizing systemic toxicity. CED of nanoliposomal-irinotecan (Onivyde) showed to be a superior delivery route for anti-tumor activity in animal models. An advance of this trial is the development and use of real time CED, which utilizes MRI to visualize the CED process with the aid of co-convected contrast agents, monitoring delivery into the brain and affording for corrective action. METHODS: This is a 3 + 3 single dose escalation trial with 2 cohorts: 20mg/ml and 40mg/ml. Onivyde and GAD were co-infused via the same catheters in a one-time delivery. The total dose was personalized based on the patient's tumor volume, and ranged from 20–680 mg of Onivyde, given via up to 4 catheters. Tumor diameters were allowed to be 1 – 4 cm, with injection volumes ranging from 2 – 17 mL of infusate. RESULTS: 13 patients have been treated on this protocol, all in under 5 hours. There were 9 GBs, 1 gliosarcoma, 2 AAs, and 1 oligoastrocytoma. Utilizing imaging software, we correlated pre-infusion modeling of the drug distribution with post-infusion imaging. A number of technical challenges were overcome by real time monitoring; the total volume of distribution (Vd), and the Vd to volume infused (Vi) ratio for each infusion was ~2. Of all patients, the only notable AE was encephalopathy, which was resolved. CONCLUSIONS: Image-guided distribution allows for safe real-time placement and adjustment of CED cannula of Onivyde into patient's brains. Such methods allow for maximum tumor coverage and warrant further studies with repeat dosing.

SCIDOT-03. HYPERLOADED POLY(2-OXAZOLINE) MICELLES AS PERSONALIZED DRUG CARRIERS FOR BRAIN TUMORS

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