(NCT03091478). This study aims to determine if pembrolizumab therapy can lead to a radiologic, cytologic or clinical response in the CNS, in patients with LMD. METHODS/STUDY POPULATION: Patients with pathologically confirmed advanced solid tumors, and either radiologic or cytologic evidence of LMD, will be identified at a single institution. Radiologic LMD will be defined as a >4 mm area of measurable LMD on gadolinium-enhanced MRI brain/total-spine; and cytologic LMD will be defined as the presence of malignant cells on CSF cytology. Patients will be excluded if they have: active autoimmune conditions that require immunosuppression, received radiation therapy to the only area of measurable LMD within 3 months of study enrollment, have an ECOG performance status <1. Once enrolled, patients will receive pembrolizumab 200 mg intravenously every 3-weeks, until disease progression or unacceptable toxicity. Patients will have CSF sample sampling, blood draws, radiologic imaging of the body (CT), brain/total-spine (gadolinium-enhanced MRI) pre-treatment, after 2 and after 4 cycles of therapy, for response assessment and correlative studies. The primary endpoint of the study is CNS response assessed at 12 weeks/after 4 cycles of pembrolizumab, defined either as radiologic response (reduction in size of LMD on gadolinium-enhanced MRI) and/or cytologic response (conversion of positive to negative CSF cytology on 2 consecutive samples) and/or clinical response. Secondary endpoints will include progression-free survival, overall survival, and safety. To explore the mechanisms by which pembrolizumab may affect LMD, we will assess dynamic changes in genomic and immunologic markers in the CSF and serum pre and post pembrolizumab using next-generation sequencing and multi-color flow cytometry, respectively. RESULTS/ANTICIPATED RESULTS: We will aim to accrue a total of 20 patients, allowing for a 10% drop-out rate, the final sample size will include 18 patients who have received at least 1 dose of pembrolizumab. CNS-response at 12 weeks will be assessed radiologically +/− cytologically, and the proportion of patients with CNS response and associated 95% confidence interval with be reported. CNS-progression-free survival and overall survival will be assessed using the Kaplan-Meier method. Cause of death will be recorded. Safety will be assessed as detailed above, and monitored as per an institutional Data Safety and Monitoring Plan. Exploratory endpoints will include genomic testing of tumor cells and cell-free DNA in CSF and serum, and immunologic studies of immune cells in CSF and serum at pre-defined timepoints. These data will be presented descriptively. We conservatively estimate that we will accrue 1 patient per month at our institution. Study duration will be approximately 24 months, allowing 18 months for accrual and 6 months for follow-up and data analysis. DISCUSSION/SIGNIFICANCE OF IMPACT: There are no currently FDA-approved therapies for patients with LMD from solid tumors. Anti-PD-1 immunotherapy is a promising class of agents, with known efficacy in patients with CNS metastatic disease, across tumor types. This study seeks to identify whether pembrolizumab may lead to CNS responses in patients with LMD. Additionally, genomic and immunologic analyses in CSF and blood pre and post-pembrolizumab may identify mechanisms by which immunotherapy affects the CNS in patients with LMD.

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Percentage of viable tumor Versus radiation treatment effect in surgical specimens is not associated with outcomes in recurrent glioblastoma

Robert D. Schwab[1], Stephen Bagley[2], Zev Binder[3], Robert Lustig[4], Donald O'Rourke[3], Steven Brem[3], Arati S. Desai[2] and MacLean Nasrallah[5]

[1] University of Pennsylvania School of Medicine, Philadelphia, PA, USA; [2] Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3] Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [4] Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5] Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

OBJECTIVES/SPECIFIC AIMS: In patients with recurrent glioblastoma (GBM) who undergo a second surgery following standard chemoradiotherapy, histopathologic examination of the resected tissue often reveals a combination of viable tumor and treatment-related inflammatory changes. However, it remains unclear whether the degree of viable tumor Versus "treatment effect" in these specimens impacts prognosis. We sought to determine whether the percentage of viable tumor Versus "treatment effect" in recurrent GBM surgical samples, as assessed by a trained neuropathologist and quantified on a continuous scale, is associated with overall survival. METHODS/STUDY POPULATION: We reviewed the records of 47 patients with histopathologically confirmed GBM who underwent surgical resection as the first therapeutic modality for suspected radiographic progression following standard radiation therapy and temozolomide. The percentage of viable tumor Versus "treatment effect" in each specimen was estimated by one neuropathologist who was blinded to patient outcomes. RESULTS/ANTICIPATED RESULTS: After adjusting for other known prognostic factors in a multivariate Cox proportional hazards model, there was no association between the degree of viable tumor and overall survival (HR 0.83; 95% CI, 0.20–3.4; $p = 0.20$). DISCUSSION/SIGNIFICANCE OF IMPACT: These results suggest that, in patients who undergo resection for recurrent GBM following standard first-line chemoradiotherapy, histopathologic quantification of the degree of viable tumor Versus "treatment effect" present in the surgical specimen has limited prognostic influence and clinical utility.

2016

Plasma microRNA markers of upper limb recovery following human stroke

Matthew A Edwardson, Xiaogang Zhong, Amrita Cheema and Alexander Dromerick

Georgetown – Howard Universities

OBJECTIVES/SPECIFIC AIMS: MicroRNAs are small, non-coding RNAs that control gene expression by inhibiting protein translation. Preclinical studies in rodent stroke models suggest that changes in microRNA expression contribute to neural repair mechanisms. To our knowledge, no one has previously assessed microRNA changes during the recovery phase of human stroke. Our goal was to determine whether patients with significant upper limb recovery following stroke have alteration of neural repair-related microRNA expression when compared to those with poor recovery. METHODS/STUDY POPULATION: Plasma was collected at 19 days post-stroke from 27 participants with mild-moderate upper extremity impairment enrolled in the Critical Periods After Stroke Study. MicroRNA expression was assessed using TaqMan microRNA assays (Thermo Fisher Scientific). Good recovery was defined as ≥ 6 point change in the Action Research Arm Test (ARAT) score from baseline to 6 months. Bioinformatics analysis compared the plasma microRNA expression profiles of participants with good Versus poor recovery. Candidate biomarkers were identified after correcting for multiple comparisons using a false discovery rate <0.05. RESULTS/ANTICIPATED RESULTS: Eleven microRNAs had significantly altered expression in the good ($n = 22$) Versus poor ($n = 5$) recovery groups, with 2 showing increased expression—miR-371-3p and miR-520g, and 9 showing decreased expression—miR-449b, miR-519b, miR--581, miR-616, miR-892b, miR-941, miR-1179, miR-1292, and miR1296. Three of these could be implicated in neural repair mechanisms. Elevated miR-371-3p levels increase the likelihood that pluripotent stem cells will differentiate into neural progenitors. MiR-892b decreases levels of amyloid precursor protein, which has been implicated as a regulator of synapse formation. Finally miR-941, the only known human-specific microRNA, downregulates the CSPα protein which is involved in neurotransmitter release. DISCUSSION/SIGNIFICANCE OF IMPACT: This preliminary study suggests that circulating microRNAs in the plasma may help serve as biomarkers of neural repair and aid in understanding human neural repair mechanisms. If validated in larger studies with appropriate controls, these markers could aid in timing rehabilitation therapy or designing recovery-based therapeutics.

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Pre-treatment sleep disturbance as a risk factor for radiation therapy induced pain in 676 women with breast cancer

Anita R. Peoples[1], Wilfred R. Pigeon[1], Dongmei Li[1], Joseph A. Roscoe[1], Sheila N. Garland[2], Michael L. Perlis[3], Vincent P. Vinciguerra[4], Thomas Anderson[5], Lisa S. Evans[6], James L. Wade III[7], Deborah J. Ossip[1], Gary R. Morrow[1] and Julie R. Wolf[1]

[1] University of Rochester Medical Center; [2] Memorial University; [3] University of Pennsylvania; [4] Northwell Health NCORP, Lake Success, NY, USA; [5] Columbus NCORP, Columbus, OH, USA; [6] Southeast Clinical Oncology Research (SCOR) Consortium NCORP, Winston-Salem, NC, USA; [7] Heartland Cancer Research NCORP, Decatur, IL, USA

OBJECTIVES/SPECIFIC AIMS: The purpose of the present secondary data analysis was to examine the effect of moderate-severe disturbed sleep before the start of radiation therapy (RT) on subsequent RT-induced pain. METHODS/STUDY POPULATION: Analyses were performed on 676 RT-naïve breast

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