THER-05. SOLITARY CEREBRAL METASTASIS FROM TRANSITIONAL CELL CARCINOMA OF THE BLADDER

Lissette Jimenez, Liliana Hanefeld-Fox, Bryan Huang, and Michael Andryka; White River Health System, Batesville, AR, USA

INTRODUCTION: Brain metastasis is the most common neurological neoplasia seen in adults. They typically metastasize from primary lung or breast but very seldom is bladder cancer the culprit. Transitional cell carcinoma (TCC) of the bladder accounts for less than 1% of brain metastasis and few cases have been reported in literature. Here we present a rare case of TCC presenting with signs of neurological impairment. CASE DESCRIPTION: A 75-year-old male with history of TCC presented to the emergency department with right upper extremity hemiparesis and dysarthria of 5 hours duration. He had undergone cystoscopy with resection of tumor 3 years prior followed by gemcitabine chemotherapy and combination radiotherapy/immunotherapy. CT imaging revealed a hyperdense 3.3 cm mass in the left frontoparietal region with internal hemorrhage measuring 1.4 cm and surrounding vasogenic edema. He was immediately treated with high dose corticosteroids and antiepileptics which did not result in improvement of his symptoms. Metastatic workup which included contrast enhanced CT of chest, abdomen and pelvis revealed no evidence of local or metastatic recurrence. Due to rapid worsening of his status, respiratory failure and encephalopathy, family did not want to pursue additional treatment and decided on inpatient hospice. The patient died 3 weeks later due to rapid neurological decline. DISCUSSION: According to literature, CNS involvement of disseminated TCC varies from 0.6% - 8%, and bladder carcinoma accounts for 0.5% of all intracranial metastases. Incidence of CNS involvement without evidence of recurrence or disseminated disease is extremely uncommon. Aggressive multitherapeutic regimens, which include gemcitabine, have been favored for its penetration of the blood-brain barrier but even with its use disease may present years later with an unfavorable prognosis. Although metastasis from TCC of the bladder is rare any decline in neurological status should warrant further investigation in these patients.

THER-06. GENOMIC AND IMMUNE CHARACTERIZATION OF TRIPLE NEGATIVE BREAST CANCER BRAIN METASTASES

Benjamin Vincent[1], Maria Sambade[1], Shengjie Chai[1], Marni Siegel[1], Luz Cuaboy[1], Alan Holye[1], Joel Parker[1], Charles Perou[1], and Carey Anders[2]; [1]University North Carolina, Chapel Hill, NC, USA, [2]Duke University Medical Center, Durham, NC, USA

INTRODUCTION: Approximately 50% of patients with metastatic triple negative breast cancer (TNBC) will develop brain metastases (BM). Routinely treated with radiotherapy and/or surgery, survival is generally less than one year. There are no approved systemic therapies to treat TNBC BM. We characterized the genomic and immune landscape of TNBC BM to foster the development of effective brain permeable anti-cancer agents, including immunotherapy. EXPERIMENTAL PROCEDURES: A clinically-annotated BCBM biobank of archival tissues was created under IRB approval. DNA (tumor/normal) and RNA (tumor) were extracted from TNBC primaries and BM; whole exome (WES) and RNA sequencing (RNASeq) was performed. Mutations were determined from WES as those co-identified by two variant callers (StrelkalCadabra). Immune gene signature expression, molecular subtype identification, and T cell receptor repertoires were inferred from RNAseq. RESULTS: 32 TNBC patient tissues (14 primaries, 18 BCBM, 6 primary-BCBM matched), characterized as basal-like by PAM50, were analyzed. Top exome mutation calls included ten genes in ≥19% of BCBMs including TP53, ATM, and PIK3R1, and four genes in ≥18% of primaries including TP53 and PIK3R1. Many immune gene signatures were lower in BM compared to primaries including B cell, dendritic cell, regulatory T cell, and IgG cluster ($p< 0.05$). A signature of PD-1 inhibition responsiveness was higher in BM compared with primaries ($p< 0.05$). BCBM T cell receptor repertoires showed higher evenness and lower read count (both $p < 0.01$) compared to primaries. CONCLUSIONS: TNBC BM compared to primaries that metastasize to the brain show lower immune gene signature expression, higher PD-1 inhibition response signature expression, and T cell receptor repertoire features less characteristic of an active antigen-specific response. Mutations common to TNBC BM and primaries include TP53 and PIK3R1. Given that non-BCBM (i.e. lung and melanoma) show response to checkpoint inhibitors, these findings collectively support further study of immunotherapy for TNBC BM.

THER-07. DEVELOPMENT OF A NEW MOLECULAR PREDICTOR FOR RISK OF BRAIN METASTASES AND EFFICACY OF TARGETED THERAPY IN MELANOMA

Howard Colman, Ken Boucher, Chris Stehn, David Kircher, and Sheri Holmen; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Despite therapeutic advances in the treatment of melanoma, development of brain metastases (BM) continues to be a major manifestation of treatment failure. The ability to identify those patients who are at highest risk of developing brain metastases is limited with current methods. Development of sensitive and specific biomarkers to predict which stage II-III melanoma patients are at highest risk of BM would enable initiation of prospective clinical trials focused on both intensive surveillance and therapeutic prevention. To accomplish this goal, we embarked on an effort to optimize a combined molecular/clinical/pathologic predictor of BM risk. We firstanalyzed multiple gene expression datasets including TCGA (n = 437) and an independent series from Australia (n = 183) and identified a list of 60 consensus genes that is robustly predictive of development of melanoma BM ($p < 0.05$; FDR 5%). Next, we performed a similar analysis of association of miRNAs and melanoma BM risk which identified a set of miRNAs with significant predictive power. An optimized combined set of mRNA and miRNA markers was a better predictor of BM risk than either mRNA or miRNA list alone when applied to the TCGA data set. The combined predictor was most sensitive in separating patients with no metastases from those with either BM or systemic metastases. Current efforts are focused on optimizing miRNA and mRNA separation of patients specifically with BM from those with other mets, and with integrating the expression classifier with other clinical and pathologic predictive factors including: age, stage, thickness, location, histology, ulceration, gender. The sensitivity and specificity of the resulting clinical/molecular predictor will be validated in an independent retrospective cohort, and subsequently implemented in a prospective BM screening trial to determine real-world utility of this approach in preparation for prospective BM adjuvant/chemoprevention trials utilizing both immunotherapy and targeted therapy approaches.

THER-08. BRAIN METASTASES AS A FIRST SITE OF RECURRENCE IN PATIENTS RECEIVING CHEMOTHERAPY WITH CONTROLLED SYSTEMIC CANCER: A CRITICAL BUT UNDER-RECOGNIZED CLINICAL SCENARIO

Kaelin O'Connell, Carlos Romo and Stuart Grossman; Johns Hopkins University, Baltimore, MD, USA

BACKGROUND: As the treatment of non-central nervous system (CNS) malignancies has improved, brain metastases (BM) have been observed as a site of first recurrence in patients with controlled or responding systemic cancers. This suggests that while chemotherapy is effective for the systemic disease, drug concentrations in the CNS are likely subtherapeutic. These findings are in accord with data suggesting that over 98% of FDA-approved drugs are unable to penetrate the blood brain barrier (BBB). METHODS: A literature review was conducted to estimate the proportion of patients with non-small lung cancer (NSCLC), breast cancer, and melanoma with controlled systemic cancers who developed BM as initial site of recurrence. Only studies explicitly reporting BM with controlled extra-cranial (EC) disease or reporting the first site of recurrence after chemotherapy were included. RESULTS: Of 262 studies screened,13 contained adequate data regarding the status of systemic cancer and initial site of recurrence. These reported on 1,024 patients. Four studies in patients with NSCLC revealed that 11–43% developed BM as initial site of recurrence. Similar data was seen in patients with breast cancer (6 studies, 4–19%) and metastatic melanoma (3 studies, 4–25%). Approximately 15% of patients on chemotherapy with stable or responding systemic NSCLC, breast cancer, and melanoma developed isolated BM as initial site of relapse. CONCLUSIONS: This literature review included 1,024 patients with common and treatable metastatic cancers whose disease was controlled with chemotherapy. First recurrence in the brain was noted in 23% of those with NSCLC, 12% with breast cancer, and 12% with melanoma. These findings strongly suggest that, while systemic antineoplastic therapy controlled their systemic cancer, concentration of these drugs within the CNS was low, allowing disease progression in the CNS. Reducing the incidence of BM requires novel therapeutic approaches designed to facilitate drug entry through an intact BBB early in treatment.

THER-09. IMPACT OF KRAS MUTATION STATUS ON THE EFFICACY OF IMMUNOTHERAPY IN LUNG CANCER BRAIN METASTASES

Adam Lauko, Assad Ali, Soumya Sagar, Addison Barnett, Hong Li, Samuel Chao, Nathan Pennell, Glen Stevens, David Peereboom, Jennifer Yu, Erin Murphy, Lilyana Angelov, Alireza Mohammadi, John Suh, Gene Barnett, and Manmeet Ahluwalia; Cleveland Clinic, Cleveland, OH, USA

BACKGROUND: Immunotherapy is increasingly used in patients with non-small cell lung cancer brain metastases (NSCLCBM). KRAS mutations are associated with worse prognosis and there is no FDA approved targeted therapy. KRAS mutations are associated with increased expression of PD-L1. We evaluated the outcomes of NSCLCBM with KRAS mutations treated with immune checkpoint inhibitors (ICI). METHODS: We reviewed 800 patients with NSCLCBM treated at our tertiary care center. 226 had known KRAS mutational status, 121 of which received immunotherapy. Overall survival (OS) was calculated from either the start of immunotherapy (when both groups received immunotherapy) or from the date of diagnosis of brain metastasis. Kaplan-Meier method and Cox Proportional hazard model were