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

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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

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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

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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

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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

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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

utilized to determine differences in OS and the Chi-square test was utilized to determine differences in PD-L1 expression. RESULTS: In 109 patients where both KRAS and PD-L1 status were known, KRAS mutations had greater PD-L1 expression (80.1% vs 61.9% positive, p=0.04). There was no difference in OS between KRAS mutant vs KRAS wild-type patients treated with immunotherapy. Median survival from the start of immunotherapy was 15.6 vs 15.5 months respectively (p=0.7), after adjusting for age, KPS, lesion number and extra-cranial metastasis (HR = .91, p=.7). Patients with KRAS mutations treated with immunotherapy versus those who received chemotherapy had a 1-year OS from the diagnosis of brain metastasis of 60.9% vs 38.7% respectively (trending towards significance, p=0.05). KRAS wild-type patients treated with immunotherapy versus those who did not receive immunotherapy had a 1-year OS from the diagnosis of brain metastasis of 61.9% vs 62.5% (p=0.85), respectively. DISCUSSION: KRAS mutations are associated with increased PD-L1 expression. Use of immunotherapy negates the poor outcomes seen traditionally in patients with NSCLCBM and KRAS mutations and it improves survival compared to use of chemotherapy. Our experience supports the use of immunotherapy in these patients.

THER-10. IMPACT OF BRAF MUTATIONAL STATUS ON THE EFFICACY OF IMMUNOTHERAPY FOR MELANOMA BRAIN METASTASES

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BACKGROUND: BRAF mutations occur in 50% of melanoma patients. Targeted agents – BRAF and MEK inhibitors and immunotherapy improve survival of melanoma patients with BRAF mutations. These agents have intracranial efficacy as shown in clinical trials. However, the efficacy of immunotherapies (immune checkpoint blockade) in melanoma brain metastases and the correlation with BRAF status is not as well characterized. METHODS: We reviewed 351 patients with melanoma brain metastases treated at our tertiary care center between 2000 and 2018, 75 of which received immunotherapy with known BRAF mutational status. Two-year, 5-year, and median overall survival (OS) was calculated from the start of immunotherapy to compare the efficacy of immunotherapy in BRAF mutant and BRAF wild type patients using the log-rank test. RESULTS: At the time of diagnosis of brain metastasis, the median age was 61 (23–87) years, median KPS was 80 (50–100), number of intracranial lesions was 2 (1–15), and 79% had extra-cranial metastases. Sixty-three patients were treated with stereotactic radiosurgery (SRS), 27 underwent whole brain radiation (WBRT) and 21 underwent surgery. When treated with immunotherapy, BRAF mutant and BRAF wild type median survival was 15.7 months (95% CI=9.4 – 42.4) and 6.9 (95% CI=4.1– 26.7) months (p-value=0.205), respectively. Two-year BRAF mutant and BRAF wild type survival was 35% (95% CI=21 – 58) and 28% (95% CI=16 – 51), and 5-year survival was 22% (95% CI=10 – 46) and 23% (95% CI=11 – 47), respectively. CONCLUSIONS: Twenty percent of patients with BRAF mutant and BRAF wild-type patients treated with immunotherapy derive a long-term benefit from immunotherapy and multimodality treatment and are alive 5 years from diagnosis of brain metastases. This was rarely seen in the pre-immunotherapy era in melanoma brain metastases. There was no difference in outcome based on the BRAF mutational status with use of immunotherapy in melanoma brain metastases.

THER-11. PEPTIDE-MEDIATED PERMEABILIZATION OF THE BLOOD-BRAIN BARRIER IMPROVES DRUG DELIVERY TO BRAIN METASTASIS

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BACKGROUND: Melanoma patients have a high risk of developing brain metastases, which is associated with a poor prognosis. The blood-brain barrier (BBB) inhibits sufficient drug delivery into metastatic lesions. We investigated the ability of a synthetic peptide (K16ApoE) to permeabilize the BBB for more effective drug treatment. METHODS: DCE-MRI was performed to study the therapeutic window of BBB opening facilitated by K16ApoE. *In vivo*and *in vitro*assays were used to determine K16ApoE toxicity and also to obtain mechanistic insight into its action on the BBB. The therapeutic impact of K16ApoE on melanoma metastases was determined together with dabrafenib, which is otherwise known not to cross an intact BBB. RESULTS: DCE-MRI exhibited an effective K16ApoE-mediated BBB opening for up to 1h. Mechanistic studies displayed a dose-dependent effect of K16ApoE caused by induction of endocytosis. At higher concentrations, the peptide also showed unspecific disturbances on plasma membranes. Combined treatment with K16ApoE and dabrafenib reduced the brain metastatic burden in mice compared to dabrafenib. We also showed by PET/CT that the peptide facilitated the delivery of compounds up to 150 kDa into the brain. CONCLUSIONS: We demonstrate a transient opening of the BBB, caused by K16ApoE, that facilitates improved drug-delivery into the brain. This improves the efficacy of drugs that otherwise do not cross the intact BBB.

THER-12. PRECLINICAL EVALUATION OF NERATINIB PLUS T-DM1 IN ORTHOTOPIC PDX MODELS OF HER2-POSITIVE BREAST CANCER BRAIN METASTASES

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Breast cancer brain metastases (BCBM) are a major cause of morbidity and mortality, despite multimodal management including surgery, radiotherapy, and systemic therapies. There is an urgent need to develop novel, efficacious alternatives. Neratinib is an orally bioavailable, irreversible pan-HER tyrosine kinase inhibitor that is FDA-approved in the extended adjuvant treatment setting for HER2-positive, early breast cancer (NCT00878709). Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate with reported single-agent activity against HER2-positive BCBM. Here, we used HER2-positive orthotopic patient derived xenograft (PDX) models of BCBM to test if combining neratinib with T-DM1 could improve tumor response. PDX cells are labelled with luciferase to allow tumor growth measurement *in vivo*. We found that neratinib is able to reduce phosphorylated HER2 in an orthotopic PDX tumor derived from HER2-positive BCBM, indicating that neratinib can cross the BBB and inhibit HER2 activation in BCBM PDX tissues. However, in both HER2-positive DF-BM354 and DF-BM355 PDX models, single agent neratinib did not block orthotopic tumor growth compared to vehicle control as monitored by bioluminescence measurements. In contrast, combined treatment of neratinib with T-DM1 significantly reduced tumor growth compared to single agent treatment with neratinib or T-DM1 at earlier time points in both models. At later time points, the combined treatment is comparable to T-DM1 alone in DF-BM354 model, but significantly prolong the survival of mice bearing DF-BM355 tumors. These data warrant further testing of neratinib alone and in combination with T-DM1 in additional BCBM PDX models to better understand drivers of resistance and susceptibility to HER2-inhibitors in HER2-positive BCBMs. Furthermore, they support the launch of a prospective clinical trial (NCT01494662) to test the efficacy and tolerability of T-DM1 in combination with neratinib in patients with progressive HER2-positive BCBM.

THER-13. IMMUNOTHERAPY VERSUS STANDARD OF CARE IN MELANOMA BRAIN METASTASES WITH KNOWN BRAF STATUS

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BACKGROUND: A mutation of the BRAF protein is seen in approximately 50% of melanoma patients. Immune checkpoint inhibitors (ICI) are standard therapy in melanoma patients independent of a patient's BRAF status. The primary objective of this study is to investigate the impact of BRAF status in patients treated with ICI compared to non-ICI systemic therapy on overall survival (OS) in patients with melanoma brain metastasis (MBM). METHODS: We reviewed 351 patients with MBM treated at our tertiary care center between 2000 and 2018. Of these, 144 had known BRAF status, 71 of which were BRAF mutant and 73 were BRAF wild-type. OS was calculated from the date of diagnosis of brain metastasis to compare the efficacy of ICI to other systemic therapies. Many of these patients received multiple lines of treatment including targeted therapies at some point during their care. The log-rank test and Cox proportional hazard model was utilized to determine differences in OS. RESULTS: Eighty-four percent of patients received local therapy that included either surgery, stereotactic radiosurgery or whole brain radiation therapy. In BRAF wild-type patients, 40 received ICI and 33 underwent non-ICI systemic therapy with a median survival (5.6 vs 7.1 months) and 2-year survival (28% vs 32%), respectively (p=0.64). Of the BRAF mutant patients, 33 received ICI and 38 did not with a median survival (17.1 vs 9.0 months) and 2-year survival (36% and 19%), respectively (p=0.014). When controlling for age, KPS, ECM, and number of lesions, BRAF mutant MBM patients treated with ICI compared to non-ICI had an OS hazard ratio, HR=0.4 (95% CI=0.21 – 0.78, p=0.0069). CONCLUSIONS: ICI therapy in BRAF mutant MBM patients results in improved OS compared to those with non-ICI systemic therapy. No such difference was observed in the BRAF wild-type cohort.