THER-14. INFLUENCE OF CLINICAL PARAMETERS ON THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER BRAIN METASTASES (NSCLCBM)

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INTRODUCTION: Non-small cell lung cancer brain metastases (NSCLCBM) patients have a dismal prognosis. Immune checkpoint inhibitors (ICI) have resulted in improved outcomes in a subset of patients, although limited information exists on the impact of ICI in patients with NSCLCBM. METHODS: We reviewed 121 NSCLCBM (2012–2018) patients treated at our tertiary care center. All patients received at least 2 cycles of ICI therapy after diagnosis of NSCLCBM. Overall survival (OS) and progression-free survival (PFS) were calculated from the start of ICI therapy to date of death, progression or last follow up. Kaplan-Meier curves were used to estimate survival and were analyzed using the Wilcoxon test. RESULTS: Median age was 62 years (39–81) and median KPS was 90. Eighty-six patient received Nivolumab, 7 Atezolizumab, 25 Pembrolizumab, and 3 patients received multiple ICI over the course of their treatment for NSCLCBM. One hundred and twelve patients underwent stereotactic radiosurgery. Nine patients were treated with ICI alone and 25 patients underwent surgical resection. Median OS for the entire cohort was 558 (303–1159) days and median PFS was 220 (114–512) days. Twenty-four patients received oral steroids within the first 28 days of ICI (median prednisone equivalent dose of 27 mg). Patients on upfront steroid therapy had a median PFS of 148 days vs 301 days in patients not on upfront steroids (p-value .0095). Complete blood count at the start of ICI was available for 87 patients and neutrophil to lymphocyte ratios (NLR) were calculated. Patients with NLR at the start of ICI above 5 (n=33) had a median overall survival of 337 days compared to 558 days when NLR was below 5 (p-value .038). CONCLUSION: Use of steroids at initiation or within first 28 days of ICI therapy and NLR of greater than 5 are associated with worse outcomes in NSCLCBM treated with ICI.

THER-15. DEVELOPING TUMOR-HOMING CYTOTOXIC HUMAN INDUCED NEURAL STEM CELL THERAPY FOR BRAIN METASTASES

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INTRODUCTION: Non-small cell lung cancer (NSCLC) and breast cancer are the most common cancers that metastasize to the brain. New therapies are needed to seek out and eradicate metastases. Genetically engineered neural stem cells (NSCs) have shown unique tumor-homing capacity, allowing them to deliver cytotoxic proteins directly to tumors. An ideal NSC drug carrier would be readily available and autologous. We have transdifferentiated human fibroblasts into induced NSCs (hiNSCs) that home to tumors and engineered the hiNSCs to release the cytotoxic protein TRAIL. Here we used intracerebroventricular (ICV) injections to deliver hiNSCs to metastatic foci. METHODS: We performed an *in vitro* efficacy co-culture assay, used *in vivo* studies to determine the migration, persistence, and efficacy of therapeutic hiNSCs against H460 NSCLC and triple-negative breast cancer MB231-Br tumors in the brain. Following the establishment of tumors in the brains of nude mice, hiNSCs were injected directly into the tumor or the ventricle contralateral to the site of tumor. The migration and persistence of hiNSCs was investigated by following the bioluminescence of the hiNSCs. The therapeutic efficacy of the hiNSCs was determined by following the bioluminescece of the tumor. RESULTS/CONCLUSION: Co-culture results demonstrated that hiNSC therapy reduced the viability of H460 and MB231-Br up to 75% and 99.8% respectively compared to non-treated controls. ICV-administered hiNSC serial imaging show that cells persisted for more than one week. Fluorescent analysis of tissue sections showed that hiNSCs co-localized with lateral and a contralateral tumors within 7 days. Using H460 and MB231-Br models, kinetic tracking of intracranial tumor volumes showed intratumoral or ICV-injected therapeutic hiNSCs reduced the growth rate of brain tumors by 31-fold and 3-fold, respectively. This work demonstrates for the first time that we can effectively deliver personalized cytotoxic tumor-homing cells through the ventricles to target brain metastases.

THER-16. EFFICACY OF UPFRONT IMMUNE CHECKPOINT INHIBITORS IN LUNG CANCER BRAIN METASTASIS

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INTRODUCTION: Immune checkpoint inhibitors (ICI) have resulted in improved outcomes in a subset of patients with lung cancer. However, data describing the efficacy of ICI in lung cancer brain metastasis (LCBM) is limited. We analyzed overall survival (OS) in patients with LCBM treated with upfront ICI, defined as having received ICI within 90 days of LCBM diagnosis, compared to non-ICI therapies. METHODS: We reviewed 665 patients with LCBM who were diagnosed between 2000 and 2018 at a major tertiary care institution. Of those patients, 240 received ICI, 164 of which received ICI after 90 days and 76 received ICI within 90 days. Propensity score (PS) was calculated using a logistic regression model including age, KPS, number of baseline brain lesions, and presence of extra-cranial metastasis (ECM) at the time of BM diagnosis. OS from BM diagnosis between PS matched cohorts were compared using Kaplan-Meier, the Log-Rank test, and Cox proportional hazards model. RESULTS: Prior to PS matching, median survival between ICI and non-ICI cohorts was not significantly different (10.9 months for both, p=0.81), although more ICI patients had ECM (57.1% vs 40.9%, p=0.006). Following PS matching, the ICI (n=76) and non-ICI (n=76) cohorts had a median age (62.4 vs 62.3 years), KPS (80 for both), lesion number (2 for both), and ECM (56.6% for both). Of matched patients, 94% received SRS, 52% received WBRT, and 29% underwent surgical resection. Compared to non-ICI, the ICI cohort has a 2-year OS hazard ratio, HR=0.87 (95% CI=0.58–1.31, p=0.51). Median and 1-year survival were not significantly different between ICI and non-ICI cohorts (median: 10.9 vs 9.1 months; 1-yr: 43.0% vs 42.4%). CONCLUSION: Patients with BM from primary lung cancer who received ICI within 90 days of their BM diagnosis did not have improvement in OS compared to patients who received non-ICI therapies.

MULTIMODALITY

MLTI-01. IMMUNOLOGICAL REPROGRAMMING IN THE CNS TUMOR MICROENVIRONMENT AND THERAPEUTIC EFFICACY OF RADIOTHERAPY WITH STAT3 BLOCKADE

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BACKGROUND: Patients with central nervous system (CNS) tumors are typically treated with radiation therapy, but this is not curative and results in the upregulation of p-STAT3 that drives invasion, angiogenesis, and immune suppression. Therefore, we investigated the combined effect of an inhibitor of the STAT3 pathway that is currently in clinical trials (WP1066) and whole-brain radiation therapy (WBRT) in murine models of CNS malignancy. METHODS: C57BL/6 mice underwent intracerebral implantation of either B16 melanoma or GL261 glioma cells, WBRT, and treatment with WP1066 a blood-brain barrier penetrant inhibitor of the STAT3 pathway or the two in combination. The role of the immune system was evaluated using tumor rechallenge strategies, immune incompetent backgrounds, immune monitoring, and nanostring gene expression analysis of 770 immune-related genes from immune cells, including those directly isolated from the CNS tumor microenvironment. RESULTS: The combination of WP1066 and WBRT resulted in long-term survivors and enhanced median survival time relative to monotherapy. Immunological memory appeared to be induced, because mice were protected during subsequent tumor rechallenge. Therapeutic efficacy was completely lost in immune incompetent mice. Extensive functional immune monitoring and nanostring profiling followed by bioinformatic processing revealed that the most robust immunological responses were located in the CNS tumor microenvironment rather than the periphery. An unbiased analysis of the immune-cell heat maps of the combination therapy relative to monotherapy were notable for upregulation of T-cell functional genes, dendritic cell function, MHC expression, and antigen presentation in the CNS tumor. These data highly suggest that antigen presentation and T-cell effector function are requirements within the tumor microenvironment of the CNS for full antitumor immune-mediated activities. CONCLUSION: This study indicates that the combination of STAT3 inhibition and WBRT enhances the therapeutic effect against established tumors in the CNS by inducing dendritic cell maturation and activation in the CNS tumor.

MLTI-02. A PHASE I TRIAL OF SORAFENIB WITH WHOLE BRAIN RADIOTHERAPY (WBRT) IN BREAST CANCER PATIENTS WITH BRAIN METASTASES AND A CORRELATIVE FLT-PET BRAIN IMAGING STUDY IN PATIENTS RECEIVING WBRT +/- SORAFENIB

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BACKGROUND: Sorafenib has demonstrated anti-tumor efficacy in breast cancer and radiosensitizing activity preclinically. [18F] 3'deoxy-3'-