EXTH-02. TUMOR-HOMING INDUCED NEURAL STEM CELL THERAPY INHIBITS THE PROGRESSION OF BREAST CANCER BRAIN METASTASIS AND LEPTOMENINGEAL CARCINOMATOSIS

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INTRODUCTION: Breast cancer brain metastasis, including leptomeningeal carcinomatosis (LC), remains one of the most lethal CNS diseases. New therapies are urgently needed to treat this highly aggressive disease. Here we used models of both breast cancer brain parenchymal metastasis and leptomeningeal metastasis to investigate the efficacy of engineered tumor-homing neural stem cells (NSCs) therapy. METHODS: Personalized NSCs were created using Sox2 overexpression to transdifferentiate human fibroblasts into induced NSCs (iNSCs), followed by genetic engineering to enable iNSCs to secrete cytotoxic TRAIL (iNSC-TRAIL). For the parenchymal metastasis study, iNSC-TRAIL therapy was infused intracerebroventricularly (ICV) into Nude mice bearing established intracranial MDA-MB-231-Br human breast cancer cells expressing fluorescent and bioluminescent reporters. For LC studies, we established the disease model by inoculating Nude mice with MDA-MB-231-Br tumor cells via intracisternal infusion. iNSC-TRAIL therapy was evaluated by infusing therapy ICV either 1 week prior to or 3 days after tumor inoculation to mirror prophylactic or established tumor treatment, respectively. Tumor progression in the brain and spine was monitored by serial bioluminescence imaging (BLI), and survival was analyzed. RESULTS: Serial BLI showed ICV-infused iNSC-TRAIL reduced parenchymal tumor volumes by 72% 3 weeks post-ICV infusion, and extended median survival from 37 to 52 days. Testing iNSC-TRAIL therapy against established LC tumors, serial BLI showed ICV iNSC-TRAIL therapy reduced established tumors 196-fold in the brain and 500-fold in the spine within 2 weeks post-infusion, while extending median survival from 25 to 47 days. In the prophylactic LC model, iNSC-TRAIL therapy markedly delayed tumor development with tumors in the brain remaining > 1000-fold smaller than control, and tumors in the spine below the limit of detection through 1 month post-treatment. The therapy also eliminated mortality through 50 days post-therapy. CONCLUSION: These data suggest iNSC therapy could be a promising treatment option for breast cancer brain metastasis patients.

EXTH-03. IODINE NANOPARTICLE RADIOTHERAPY OF HUMAN BREAST CANCER GROWING IN THE BRAINS OF ATHYMIC MICE

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About 30% of breast cancers metastasize to brain; those widely disseminated are fatal typically in 3–4 months, even with the best available surgery, drugs, and radiotherapy. To address this dire situation, we have developed iodine nanoparticles (INPs) that target brain tumors after intravenous (IV) injection. The iodine then absorbs X-rays during radiotherapy (RT), creating free radicals and local tumor damage, effectively boosting the local RT dose at the tumor. Efficacy was tested using the very aggressive human triple negative breast cancer (TNBC, MDA-MB-231 cells) growing in the brains of athymic nude mice. With a well-tolerated non-toxic IV dose of the INPs (7 g iodine/kg body weight), tumors showed a heavily iodinated rim surrounding the tumor having an average uptake of 2.9% iodine by weight (peaks at 4.5%), calculated to provide dose enhancement factors of ~5.5 (peaks at 8.0) -- the highest ever reported for any radio-sensitizing agents. With 15 Gy, single dose RT, all animals died by 72 days; INP pretreatment resulted in longer-term remissions with 40% of mice surviving 150 days and 30% surviving > 280 days. Fluorescence confocal microscopy revealed most INP staining co-localized with CD31in the tumor center and periphery. Greatest INP/CD31 staining was in the tumor periphery, the region of increased MicroCT contrast. Tumor cells line irregularly-shaped spaces (ISS) with INP, CD31 staining very close to or on the tumor cell surface and PAS stain on their boundary and may represent a unique form of CD31-expressing vascular mimicry in intracerebral 231-tumors. INP/CD31 co-staining is also seen around ISS formed around tumor cells migrating on $CD31^{+}$blood-vessels. The significant radiation dose enhancement to the prolific INP-binding ISS found throughout the tumor but concentrated in the tumor rim, may contribute significantly to the life extensions observed after INP-RT; VM could represent a new NP, particularly INP, tumor-homing target.

EXTH-04. INTRATHECAL (IT) DELIVERY OF TYPE I POLARIZED DENDRITIC CELL VACCINE (DC1) ERADICATES TUMOR GROWTH IN BREAST CANCER (BC) XENOGRAFT MODEL WITH BRAIN METASTASES (BM) AND LEPTOMENINGEAL DISEASE (LMD)

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BACKGROUND: Approx. 5% of BM will also develop LMD. Currently there is no effective treatment for BC-associated BM/LMD. As systemic therapies do not prevent the disease recurrence and eventual death, the better option would be direct-targeted approach. We have shown that there is a loss of the anti-HER2 and anti-HER3 CD4 Th1 immune response in BC patients (pts). In a clinical setting, administration of class II HER2 peptide-pulsed Type I polarized dendritic cell vaccine (HER2-DC1) partially restored anti-HER2 Th1 immune responses with pathologic complete response in HER2+ BC patients. In this study, we examined the IT delivery of HER2/HER3- DC1 in BC-LMD model. METHODS: Luciferase-labeled HER2+ TUBO BC cell line was injected into the cisterna magna of BALB/c mice to develop BM/LMD. We developed a technique, coined the "Top Hat" (TH) for mouse model that mimics the Ommaya reservoir in BC-pts. The TH essentially allows us to administer IT treatment directly into CSF. BC-BM/LMD bearing mice were given HER2- and Her3 peptide-pulsed Type I polarized DC1 through the TH. RESULTS AND DISCUSSION: BM/LMD mice were randomized into following groups: 1) systemic Her2-DC1 2) IT Her2-DC1 3) IT Her2-/Her3-DC1. The median survival (MS) of control mice was 10 days and systemically treated mice was 19 days. IT Her2-DC1 animals did significantly better than both control and systemic treated groups (MS: 63 days; $p< 0.0001$) and overall survival (OS): 44%. Interestingly, mice given IT Her2-/Her3-DC1 had the best OS (78%). Surviving animals were eventually disease free. Mice that had complete tumor regression were immune to subsequent rechallenge with TUBO cells. Immune cell infiltration in the of CSF, spinal cord and tissues of experimental mice are currently ongoing. CONCLUSIONS: Our preclinical data supports the clinical relevance of using intrathecal delivery of DC1 vaccine as a potential treatment for BM and LMD of BC-pts.

EXTH-05. NON-CYTOTOXIC RADIATION ENHANCES DELIVERY OF ANTISENSE OLIGONUCLEOTIDES AND IMPROVES CHEMO-RADIATION EFFICACY IN BRAIN TUMOR XENOGRAFTS

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Overexpression of O^6-methylguanine DNA methyltransferase (MGMT) contributes to brain tumor chemo-resistance. Previously we found that non-cytotoxic radiation improved anti-MGMT Morpholino Oligonucleotides (AMONs) delivery to reduce MGMT levels in subcutaneous tumor xenografts. Here we evaluated if radiation enhanced the delivery of intravenous (IV) AMONs to rat brain and improved chemo-radiation therapy (CRT) efficacy using rat models of human brain tumors. Athymic nude rats bearing orthotopic cerebellar D283 medulloblastoma or intracerebral H460 non-small cell lung carcinoma (NSCLC) brain metastasis xenografts were used. The impact of cranial radiation on delivery of IV 3'-carboxyfluorescein labeled oligonucleotides across the neurovascular unit was evaluated using confocal microscopy. We found that high brain parencymal fluorescence in radiated compared to non-radiated rats. MGMT protein silencing was assessed by immunoblot in tumor-bearing rats 3 d after 2 Gy cranial radiation alone or followed in 1 d by IV AMONs (10.5 mg/kg). Radiation followed by AMONs reduced MGMT expression by 50% in both xenograft models. To evaluate efficacy, tumor-bearing rats received one dose of 2 Gy radiation plus oral temozolomide (20 mg/kg x 4d) with or without IV AMONs. AMONs concurrent with CRT reduced tumor volumes in the medulloblastoma model ($p=0.012$), and a similar trend was found in the NSCLC brain metastasis model. In conclusion, we demonstrate the use of a single clinically relevant radiation dose fraction to guide and enhance the delivery of oligonucleotides into brain tumor xenograft models to reduce MGMT levels and improve CRT efficacy.

EXTH-06. INTEGRATED MOLECULAR PROFILING REVEALS TARGETABLE MOLECULAR ABNORMALITIES SHARED ACROSS MULTIPLE HISTOLOGIES OF BRAIN METASTASIS

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Brain metastases (BMs) occur in approximately 20–40% of patients with advanced cancer, and the estimated prevalence of new BMs in United States is between 200,000–300,000 per year. While the incidence of BM has increased over the past decades due to improvements in brain tumor detection technology, the prognosis is still very poor with the median overall survival times from weeks to few months. Therefore, identification of the precise molecular landscape and therapeutic targets for BMs is absolutely essential in tangible improvement of patient management. Here, we performed integrated genomic, transcriptional, and proteomic profiling in a cohort of lung, breast, and renal cell carcinomas consisting of both BMs and patient-matched primary or extracranial metastatic tissues to iden-