Title

TAMI-01. NEOADJUVANT PD-1 ANTIBODY BLOCKADE REMODELS THE IMMUNE MICROENVIRONMENT OF METASTATIC BRAIN TUMORS

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we confirmed the complete loss of fluorescence on the tumor resected bed. We check the MRI within 48 hour after operation and assess the extent of resection. RESULTS: Among the 26 patients, 22 patients were confirmed glioblastoma and 3 anaplastic astrocytoma and 1 anaplastic oligoastrocytoma. We confirmed all enhancing lesion was completely removed, however, 4 patients show residual non-enhancing lesion in post-operative MRI. Two patients suffered temporary hemiparesis and 2 patients show permanent visual field defect. CONCLUSION: 5-ALA is useful tool for glioma surgery. Resection extent could be increased, however, non-enhancing lesion in the high grade gliomas, might be missed under 5-ALA guidance.

SURG-40. SURGICAL RESECTIONS IN BROCA'S AREA DO NOT LEAD TO BROCA'S APHASIA

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Brodmann's areas 44/45 of the inferior frontal gyrus (IFG), are the seat of Broca's area. The Western Aphasia Battery is a commonly used language battery that diagnoses aphasias based on fluency, comprehension, naming and repetition. Broca's aphasia is defined as low fluency (0-4/10), retained comprehension (4-10/10), and variable deficits in repetition (0-7.9/10) and naming (0-8/10). The purpose of this study was to find anatomic areas associated with Broca's aphasia. Patients who underwent resective brain surgery in the dominant hemisphere were evaluated with standardized language batteries pre-op, POD 2, and 1-month post-op. The resection cavities were outlined to construct 3D-volumes of interest. These were aligned using an affine transformation to MNI brain space. A voxel-based lesion-symptom mapping (VLSM) algorithm determined areas associated with Broca's aphasia when incorporated into a resection. Post-op MRIs were reviewed blindly and percent involvement of pars orbitalis, triangularis and opercularis was recorded. 287 patients had pre-op and POD 2 language evaluations and 178 had 1 month post-op language evaluation. 82/287 patients had IFG involvement in resections. Only 5/82 IFG resections led to Broca's aphasia. 11/16 patients with Broca's aphasia at POD 2 had no involvement of IFG in resection. 35% of IFG resections were associated with non-specific dysnomia and 36% were normal. By one-month, 76% of patients had normal speech. 80% of patients with Broca's aphasia at POD 2 improved to normal speech at 1-month, with 20% improved to non-specific dysnomia. The most highly correlated ($P < 0.005$) anatomic areas with Broca's aphasia were juxtasylvian pre- and post-central gyrus extending to supramarginal gyrus. While Broca's area resections were rarely associated with Broca's aphasia, juxtasylvian pre- and post-central gyri extending to the supramarginal gyrus were statistically associated with Broca's type aphasia when resected. These results have implications for planning resective brain surgery in these presumed eloquent brain areas.

SURG-41. BLOOD-BRAIN BARRIER DISRUPTION WITH HIGH-FREQUENCY ELECTROPORATION IN VIVO: A PRELIMINARY INVESTIGATION DEMONSTRATING THE EFFECTS OF VARIED PULSE WIDTHS AND INTRA-PHASE DELAYS

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OBJECTIVE: Treatment of CNS disorders suffer from the inability to deliver large therapeutic agents to the brain parenchyma due to protection from the blood-brain barrier (BBB). High-frequency electroporation (HFE) employs a series of high voltage pulsed electric fields to disrupt the BBB and/or ablate tumor tissue while sparring proteinaceous structures. Pulsing parameters pulse width and intra-phase delay can be modulated to reduce excitation of muscle and nervous tissues, though this is inherently accompanied by an increase in thresholds for ablation in non-CNS tissues. Here, we investigate the effects of pulse width and intra-phase delay on intracranial tissue for BBB disruption (BBBD) in an in vivo healthy rodent model. METHODS: 18 male Fisher rats underwent craniectomy procedure and two blunt tipped monopolar electrodes were advanced into the brain for HFE therapy. 200 bursts of HFE were delivered at a voltage-to-distance ratio 600 V/cm. BBBD was verified with contrast enhanced T1W MRI (gadopentetate dimeglumine) and pathologically (Evans blue dye). RESULTS: Gross pathological sections and contrast enhanced T1W scans demonstrated BBBD for 2-2-2 µs (n = 4, 36.6 ± 9.4 mm^3, 36.7 ± 13.0 mm^3), 2-5-2 µs (n = 4, 74.1 ± 7.7 mm^3, 74.7 ± 9.8 mm^3), 5-2-5 µs (n = 4, 53.9 ± 8.1 mm^3, 59.2 ± 10.8 mm^3), 5-5-5 µs (n = 4, 81.2 ± 7.9 mm^3, 84.1 ± 8.7 mm^3), and 10-1-10 µs (n = 2, 61.0 ± 2.8 mm^3, 60.0 ± 4.2 mm^3) HFE. Histologically, tissue damage was restricted to electrode insertion tracks. BBBD was induced with minimal muscle contractions and minimal cell death attributed to HFE. Numerical modeling indicated the threshold for HFE-mediated BBBD as low magnitude electric fields (< 201 V/cm). These data suggest HFE-mediated BBBD is only modestly affected by changes in pulse width and intra-phase delay.

SURG-42. SAFETY OF INTRA-ARTERIAL CHEMOTHERAPY WITH OR WITHOUT OSMOTIC BLOOD BRAIN BARRIER DISRUPTION IN TREATMENT OF BRAIN TUMORS

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BACKGROUND: Intra-arterial route of drug delivery (IA) without or with osmotic blood brain barrier disruption (IA/BBBD) is one of the available techniques to overcome the blood-brain barrier and enhance drug delivery to brain tumors. We present a large single institution safety data of IA or IA/BBBD. METHODS: This is a retrospective review of the electronic records, imaging and complications in patients who underwent IA or IA/BBBD in OHSU between December, 1997 and November, 2018. Procedural complications were documented prospectively and reviewed in the electronic medical records. Toxicities, attributed to chemotherapy, were reported when grade is either II or higher by Common Terminology Criteria for Adverse Events (CTCAE). RESULTS: Complications related to chemotherapy and procedure were reported separately. Total of 4940 procedures (1102 IAC and 3838 oBBBD) were performed on 436 patients (190 female and 246 male). Pathologies were primary central nervous system lymphoma (PCNSL) (n=115, 26%), secondary central nervous system involvement (SCNSL) (n=37, 8%), glioblastoma (n=79, 18%), astrocytoma (grade II/III) (n=34, 7%), oligodendroglioma (n=64, 14%), pilocytic astrocytoma (n=10, 2%), metastatic (n=38, 8%), embryologic (n=37, 8%), others (n=22, 5%). Procedural complications: groin related (n=16, 0.32%), transient neurological decline (n=57, 1.15%), subintimal arterial injury (n=13, 0.26%), asymptomatic imaging changes (T2 or DWI) (n=60, 1.21%), symptomatic stroke (n=21, 0.43%), myocardial infarction (n=3, 0.37%), cervical cord injury (n=6, 0.12%), death within 3 days (n=6, 0.12%). Minor complications are 2.86%, major complications are 1.12%. Eighty-four percent (n=369) of the patients experienced grade 2 or higher toxicities attributed to chemotherapy. CONCLUSION: We present the largest safety data set to date from a single institution experience using IA and IA/BBBD for brain tumors. Our results suggest that IA and IA/BBBD is safe and can be performed multiple times in the same patients with acceptable procedure related complications. Efficacy of this approach is being evaluated in prospective clinical trials.

SURG-43. APPLICATIONS AND RESTRICTION OF 980NM DIODE LASER FOR BRAIN TUMOR MICROSURGERY - A PIONEER CASE SERIES AND A CRITICAL REVIEW

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BACKGROUND: Quality of life is essential for oncological patients. There are several tools that help surgery become more precise with less morbidity. Diode laser can cut and coagulate through thermal effect being helpful during surgery. It is a precise and useful technology that improves outcomes in neurooncology. OBJECTIVES: To describe a pioneer case series of oncological use of diode laser and main applications of several types of laser in neurooncology. METHODS: Detailed description of a pioneer case series of oncological patients that undergone to neurosurgical laser assisted procedures. An interventional longitudinal prospective study was conducted. Patients that had as mainly hypothesis the diagnosis of glioma or meningioma were selected. Also it was performed an extensive literature review about lasers in neurosurgery with special focus in diode laser. RESULTS: There was not any paper describing the use of diode laser in neurooncology. The 980nm diode laser was used in 15 patients. The device had an easy handling. Decreased intra-operative time for hemostasis, lesser blood loss requiring less blood transfusion was observed. No post-operative complications occurred. CONCLUSIONS: Diode laser is a useful tool for brain tumor surgery especially concerning hemostasis, providing decreased blood loss with lesser intra-operative duration. Surgical site coagulation is more effective causing less damage to adjacent structures specially in gliomas near eloquent regions. We consider this technique as a suitable adjuvant therapy for brain tumor surgeries providing an excellent hemostasis and helping cutting and vaporize lesion. This device makes surgery safer and decrease oncological morbidity.

TUMOR MICROENVIRONMENT/ANGIOGENESIS/ METABOLISM/INVASION

TAMI-01. NEOADJUVANT PD-1 ANTIBODY BLOCKADE REMODELS THE IMMUNE MICROENVIRONMENT OF METASTATIC BRAIN TUMORS

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Brain metastases (BM) commonly arise in patients with melanoma, lung, and breast cancer. Currently, there are limited options for GBM and BM patients who have failed the first-line standard treatment, underscoring the importance of developing new therapeutic strategies. Last year, we and other groups evaluated the neoadjuvant timing of anti-PD-1 checkpoint blockade therapy in recurrent GBM (rGBM) patients, which resulted in a modest survival benefit. In light of the known effectiveness of anti-PD-1 as a systemic therapy to control melanoma and non-small cell lung cancer BM, we set out to study the anti-tumor immune response of BM patients to anti-PD-1 in the neoadjuvant setting. We posited that neoadjuvant anti-PD-1 in patients with BM would result in a stronger antitumoral immune response, which could be quantified at the single cell level. To test this, we made use of contemporary single cell techniques, including multiplex immunofluorescence, time-of-flight mass cytometry (CyTOF) and single-cell RNA sequencing (scRNAseq), to characterize the intratumoral immune cell populations and their transcriptomic profiles. We found that neoadjuvant anti-PD-1 significantly increased the number of tumor infiltrating T lymphocytes in BM compared to rGBM (2.5 fold in BM, p= 0.02 vs. 1.4 fold in rGBM, p= 0.19). Multiplex immunofluorescence analysis of T cells in BM samples revealed a change from T cell exclusion to a diffusely infiltrating phenotype after anti-PD-1 treatment. Importantly, BM showed a higher fraction of effector/cytotoxic T cells compared to rGBM (7.3% vs. 0.9% of lymphoid cells, p= 0.005) and anti-PD-1 further enhanced this population. In the myeloid compartment of BM, neoadjuvant anti-PD-1 increased the frequency of HLA-DR+CD206- M1-like macrophages, implicating a pro-inflammatory microenvironment. In summary, our study delineated the immune cell subtypes altered by neoadjuvant anti-PD-1 and offers insights into new combination therapies that can help understand the clinical efficacy of immunotherapy for BM and GBM patients.

TAMI-02. ALTERATIONS IN C-X3-C MOTIF CHEMOKINE RECEPTOR 1 (CX3CR1) EXPRESSION INFLUENCE MICROGLIAL AND MACROPHAGE RESPONSE IN DIFFERENT STEPS OF CEREBRAL METASTASIS FORMATION

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Metastasis to the brain is a frequent complication in lung cancer and is still associated with a dismal prognosis. Current treatment strategies not only target tumor cells but also focus on cells of the tumor microenvironment like tumor associated microglia/macrophages (TAMs). The interactions between tumor cells and TAMs during different steps of cerebral metastasis formation of lung cancer brain metastasis are poorly characterized. Moreover, the role of CX3CR1 in this process remains unclear. We established a syngeneic cerebral metastasis mouse model by combining a chronic cranial window and two-photon laser scanning microscopy (TPLSM), which allows the tracking of single fluorescent metastasizing tumor cells and the tumor microenvironment on a cellular resolution *in vivo*over time for a period of weeks. Transgenic CX3CR1 proficient and deficient mice ($CX3CR^{GFP/wt}$ and $CX3CR1^{GFP/GFP}$) were injected with red fluorescent Lewis lung carcinoma cells. During different steps of metastasis formation (extravasation, formation of micro- and macrometastasis) the density and cell body volume of TAMs, their interaction with tumor cells and possible influence on the fate of single metastatic tumor cells were investigated using serial TPLSM. We found that during metastasis formation TAM density was significantly lower in CX3CR1 deficient mice. However, activation as assessed by TAM morphology did not differ in the absence of CX3CR1. Strikingly, CX3CR1 deficiency was associated with a significant increase of tumor cells successfully extravasating the cerebral vasculature. However, subsequent steps (mirco- and macrometastasis formation) were observed less frequent in CX3CR1 deficient mice. In summary, our results highlight a complex role of CX3CR1 for TAMs during cerebral metastasis formation, indicating anti-tumorous properties of CX3CR1 at early steps and possible protumorous effects at later stages (micro- and macrometastasis formation).

TAMI-03. IDENTIFICATION OF NOVEL DRIVERS OF LUNG-TO-BRAIN METASTASIS THROUGH IN VIVO FUNCTIONAL GENOMICS

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Brain metastasis, the most common tumor of the central nervous system, occurs in 20-36% of primary cancers. In particular, 40% of patients with non-small cell lung cancer (NSCLC) develop brain metastases, with a dismal survival of approximately 4-11 weeks without treatment, and 16 months with treatment. This highlights a large unmet need to develop novel targeted therapies for the treatment of lung-to-brain metastases (LBM). Genomic interrogation of LBM using CRISPR technology can inform preventative therapies targeting genetic vulnerabilities in both primary and metastatic tumors. Loss-of-function studies present limitations in metastasis research, as knocking out genes essential for survival in the primary tumor cells can thwart the metastatic cascade prematurely. However, gene overexpression using CRISPR activation (CRISPRa) has the potential for overcoming dependencies of gene essentiality. We theorize that an *in vivo* genome-wide CRISPRa screen will identify novel genes that, when overexpressed, drive LBM. We have developed a patient-derived orthotopic murine xenograft model of LBM using primary patient-derived NSCLC cell lines (termed LTX cells) from the Swanton Lab TRACERx study. We are now poised to transduce LTX cells with a human genome-wide CRISPRa single guide RNA (sgRNA) library, and to subsequently inject the cells into the lungs of immunocompromised mice. We will then track the process of LBM using bioluminescent and MRI imaging until mice reach endpoint. Sequencing of primary lung tumors and subsequent brain metastases promises to uncover enriched sgRNAs, which may represent novel drivers of primary lung tumor formation and LBM. To the best of our knowledge, this study is the first *in vivo* genome-wide CRISPRa screen focused on identifying novel drivers of LBM, and can inform future preventative therapies to improve survival outcomes for NSCLC patients.

TAMI-04. TUMOR TREATING FIELDS (TTFIELDS) HINDER GLIOMA CELL MOTILITY THROUGH REGULATION OF MICROTUBULE AND ACTIN DYNAMICS

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The ability of glioma cells to invade adjacent brain tissue remains a major obstacle to therapeutic disease management. Therefore, the development of novel treatment modalities that disrupt glioma cell motility could facilitate greater disease control. Tumor Treating Fields (TTFields), encompassing alternating electric fields within the intermediate frequency range, is an anticancer treatment delivered to the tumor region through transducer arrays placed non-invasively on the skin. This novel loco-regional treatment has demonstrated efficacy and safety and is FDA-approved in patients with glioblastoma and malignant pleural mesothelioma. TTFields are currently being investigated in other solid tumors in ongoing trials, including the phase 3 METIS trial (brain metastases from NSCLC; NCT02831959). Although established as an anti-mitotic treatment, the anti-metastatic potential of TTFields and its effects on cytoskeleton rapid dynamics during cellular motility warrant further investigation. Previous studies have demonstrated that TTFields inhibits metastatic properties of cancer cells. Identification of a unifying mechanism connecting the versatile TTFields-induced molecular responses is required to optimize the therapeutic potential of TTFields. In this study, confocal microscopy, computational tools, and biochemical analyses were utilized to show that TTFields disrupt glioma cellular polarity by interfering with microtubule assembly and directionality. Under TTFields application, changes in microtubule organization resulted in activation of GEF-H1, which led to an increase in active RhoA levels and consequent focal adhesion formation with actin cytoskeleton architectural changes. Furthermore, the optimal TTFields frequency for inhibition of invasion in glioma cells was 300 kHz, which differed from the optimal anti-mitotic frequency leading to glioma cell death of 200 kHz. The inhibitory effect of TTFields on migration was observed at fields intensities of 0.6 V/cm RMS (below the threshold of 1 V/cm RMS previously reported for cytotoxic effects). Together, these data identify discrete TTFields effects that disrupt processes crucial for glioma cell motility.

TAMI-05. THE IRRADIATED BRAIN MICROENVIRONMENT SUPPORTS GLIOMA STEMNESS AND SURVIVAL VIA ASTROCYTE-DERIVED TRANSGLUTAMINASE 2

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The highest-grade gliomas invariably recur as incurable tumors following standard of care comprising surgery, radiotherapy, and chemotherapy. The majority of the recurrent tumors form within the area of the brain receiving high-dose irradiation during treatment of the primary tumor, indicating that the recurrent tumor forms in an irradiated microenvironment. The tumor microenvironment has been demonstrated to influence the therapeutic re-