IMMU-51. NEUROLOGIC IMMUNE-RELATED ADVERSE EVENTS MIMICS, RISK FACTORS, AND MECHANISMS: CLIPPERS AND ASEPTIC MENINGITIS

Carlen Yuen, Kourosh Rezania, Deric Park, and Anthony Reder; University of Chicago, Chicago, IL, USA

Neurological immune-related adverse events (irAEs) are rare toxicities that occur following immune checkpoint blockade. It is imperative to distinguish between irAEs and their mimics for successful treatment. We present the first case of CLIPPERS-like lesions in a patient with thymic cancer, thymoma, and a family history of neuromyelitis optica, following treatment with pembrolizumab. The brainstem lesion was in the anatomic location of the respiratory and cardiac centers. We also present a second case of aseptic meningitis irAE in a patient with prior graft-versus-host-disease following a single dose of nivolumab. These cases add to the growing evidence of CNS complications from immune checkpoint inhibitors. Risk factors for irAEs are not well established, and we explore potential risk factors and a possible mechanism from dysfunctional regulatory T cells.

IMMU-52. IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY (ICANS) AMONG PEDIATRIC AND AYA PATIENTS: MD ANDERSON CANCER CENTER EXPERIENCE

Brandon Brown, Kris Mahadeo, Sajad Khazal, Demetrios Petropoulos, Priti Tewari, John Slopis, Paolo Tambaro, and Zsila Sadighi; The University of Texas MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION: Immune effector cell associated neurotoxicity (ICANS) and cytokine release syndrome (CRS) are potentially life-threatening complications associated with immune effector cell (IEC) therapies. We characterize ICANS in pediatric and adult young adolescent (AYA) patients receiving IEC therapy at our institution. METHODS: We reviewed clinical characteristics and severity (based on ASTCT Consensus Criteria) in pediatric and AYA patients who received IEC products from 2018–2019 at MDACC. RESULTS: Nine patients, median age 15.5 (range: 3–25) years received chimeric antigen receptor (CART) IEC therapy. Four (44%) developed ICANS within median of 8 (range: 3–27) days of CAR T cell infusion and median 6 (range: 2–7) days after CRS. Primary diagnoses were pre-B cell acute lymphoblastic leukemia (8) and mediastinal large B-cell lymphoma (1). Median CRS and ICANS severity grade was 2 (range 1–4). Symptoms included altered mental status (AMS) (5), seizure (1), aphasia (2), impaired ability to write a standard sentence (4). Neuroimaging did not correlate to ICANS symptoms or severity. EEG was performed in 3 and 1 had background slowing correlating with aphasia. CSF was obtained in two revealing lymphocytosis. All received prophylactic anti-epileptic medication and tocilizumab for concomitant CRS. Three received steroids. CONCLUSION: ICANS may present in almost half of pediatric patients within one week of receiving CART products associated with CRS. CAR-T trafficking into the CSF may explain pleocytosis in the CSF. Prospective studies may clarify. Impaired ability to write a standard sentence and the Cornell Assessment of Pediatric Delirium (CAPD) may be early indicators of ICANS in pediatric/AYA patients.

IMMU-53. CHARACTERIZATION OF THE GENOMIC AND IMMUNOLOGICAL DIVERSITY OF MALIGNANT BRAIN TUMORS THROUGH MULTI-SECTOR ANALYSIS

Max Schaettler, Megan Richters, Malachi Griffith, and Gavin Dunn; Washington University School of Medicine, St. Louis, MO, USA

While the degree of spatial genomic heterogeneity within primary glioblastoma (GBM) has been previously investigated, the extent of this heterogeneity in other malignant brain tumors and its connection to the local immune microenvironment remains unknown. To address this, we performed whole-exome, RNA, and TCR sequencing on multiple spatially distinct sectors from a cohort of malignant brain tumors comprised of both brain metastases and primary and recurrent GBMs. Our results suggest a striking difference in which a majority of mutations and predicted neoantigens are shared between spatially distinct regions of metastatic brain tumors in contrast to the spatial heterogeneity observed within both primary and recurrent GBMs. Additionally, despite substantial differences in immunotherapy responsiveness between brain metastases and GBM, we can detect significantly expanded T-cell clonotypes within both tumor types with some clonal frequencies exceeding 10% of intratumoral T-cells. Similar to the observed distribution of variants and neoantigens, the expanded clonotypes are more shared among spatially distinct sectors in metastatic brain tumors than in primary or recurrent GBMs. Interestingly, the frequencies of most of these enriched T-cell clones are significantly diminished within expanded tumor infiltrating lymphocyte (TIL) cultures, advising caution in the use of expanded TIL for the detection of tumor-specific responses. These results provide novel insight into the immunogenomic landscape of malignant brain tumors with implications for our understanding of tumor-immune interactions and the development of immunotherapies.

IMMU-55. GD2 IS A MACROPHAGE CHECKPOINT MOLECULE AND COMBINED GD2/CD47 BLOCKADE RESULTS IN SYNERGISTIC EFFECTS AGAINST GD2 POSITIVE MALIGNANCIES

Johanna Theruvath[1], Christopher Mount[1], Michelle Monje[2], Crystal Mackall[1], and Robbie Majzner[1]; [1]Stanford University, Stanford, CA, USA, [2]Stanford University School of Medicine, Palo Alto, CA, USA

GD2 is a disialoganglioside expressed on a variety of tumors including DIPG, neuroblastoma and osteosarcoma. Anti-GD2 antibodies have demonstrated some success in neuroblastoma and they have either not proven to be effective or have not been evaluated in other GD2 positive malignancies. CD47 is the dominant "Don't Eat Me" signal expressed by cancer cells to inhibit macrophages and blocking CD47 leads to phagocytosis of tumor cells. We hypothesized that CD47 blockade synergizes with anti-GD2. We measured *in vitro* phagocytosis of DIPG and NBL cells and observed a synergy of anti-GD2/CD47 compared to the single agents. *In vivo*, this combination led to the complete clearance of both orthotopic and metastatic models of NBL. Additionally, the combination significantly enhanced survival of OS xenografts. Finally, in a murine model of metastatic pulmonary OS, the combination led to a near elimination of all metastatic burden. To understand the underlying biologic basis, we studied the effects of GD2 crosslinking on tumor cells and the effects of GD2 blockade on macrophages. A portion of DIPG or NBL cells die when treated with dinutuximab, and those that survive upregulate surface calreticulin, an important pro-phagocytic ("Eat Me") signal. Additionally, we have identified the ligand for GD2, a molecule expressed on macrophages known to inhibit phagocytosis. In summary, we have identified a novel combination of anti-GD2 and anti-CD47 antibodies that is highly effective in preclinical models and will soon be tested in children. Furthermore, we have shown that GD2 itself is a macrophage checkpoint or "Don't Eat Me" signal.

INNOVATIONS IN PATIENT CARE

INNV-01. NEUROLOGIC IMPROVEMENT WITH CORTICOSTEROIDS PRIOR TO SURGERY IS PREDICTIVE OF DURABLE POST-OPERATIVE IMPROVEMENT IN MOTOR DEFICITS DUE TO BRAIN METASTASES

Stephen Bowden, Barry Cheaney II, Nasser Yaghi, Daniel Munger, Christian Lopez Ramos, Emma Richie, Matthew Wood, Ahmed Raslan, Justin Cetas, Aclan Dogan, and Seunggu Han; Oregon Health and Science University, Portland, OR, USA

Corticosteroids reduce vasogenic cerebral edema and are thought to improve related neurologic deficits or symptoms of increased intracranial pressure. Brain metastases are typically associated with a large amount of edema and, consequently, come with a disproportionate degree of mass effect that may cause such deficits. There remains no standard approach to pre-operative corticosteroid therapy, nor is it understood what clinical characteristics are associated with a neurologic response to pre-operative steroids. We examined characteristics of steroid responders versus non-responders and, further, evaluated whether a response to preoperative steroids is predictive of durable improvement in neurologic function. Patients with pathology-proven brain metastases who underwent open surgical resection between 2009 and 2019 were identified from departmental records. Charts were reviewed to identify patients with motor dysfunction who received corticosteroids prior to surgery. Multiple patient and clinical characteristics were extracted and compared using student t-, chi-square, and Fisher's exact tests. 90 patients exhibited pre-operative motor deficits, 69 of whom received corticosteroids prior to surgery (dose 2 – 112 mg; median 25 mg). 34 patients neurologic function improved prior to surgery, whereas 35 patients had no demonstrable improvement. All 34 patients (100%) whose motor function improved pre-operatively with steroids had sustained improvement at follow-up, whereas 27 of 35 (77%) patients who did not improve pre-operatively were better at follow-up ($p = 0.005$). All other clinical characteristics were similar between responders and non-responders. All motor deficits related to brain metastases that responded to steroids prior to surgery demonstrated durable improvement at follow-up, suggesting such an improvement portends a favorable long-term functional outcome. Conversely, a failure to improve with steroid therapy confers a more guarded prognosis.

INNV-02. RADIOGRAPHIC CHARACTERISTICS AND STEROID USAGE IN LASER INTERSTITIAL THERMAL THERAPY VERSUS MEDICAL MANAGEMENT FOR BIOPSY-PROVEN RADIATION NECROSIS AFTER STEREOTACTIC RADIOSURGERY OF BRAIN METASTASES

Ethan Srinivasan[1], Eric Sankey[2], Matthew Grabowski[3], Andrew Griffin[2], Elizabeth Howell[1], Balint Otvos[3], Vadim Tsvankin[2], Ahmet Atik[3], Krishna Joshi[3], Gene Barnett[3], Peter Fecci[2], and Alirezza Mohammadi[3];