Title

IMMU-27. LONG TERM STABILIZATION OF RECURRENT HIGH-GRADE GLIOMA WITH PD-1 INHIBITOR PEMBROLIZUMAB IN TWO CASES

Journal

Neuro-Oncology, 23(Supplement_6)

ISSN

1522-8517

Authors

Moldenhauer, Matthew
Du, Steven
Fu, Dan
et al.

Publication Date

2021-11-12

DOI

10.1093/neuonc/noab196.386

Peer reviewed

was determined through introduction into a T cell hybridoma, identifying a top candidate based upon a high degree of cytokine production and specificity for the mutant epitope. A TCR transgenic mouse was then generated in which more than 90% of all T cells were CD8 T cells bearing this mImp3-specific TCR. T cells isolated from this mouse display specificity for the mImp3 peptide and display *in vitro* reactivity to GL261 and other cell lines in a mImp3-dependent manner. Therefore, this model represents the first TCR transgenic targeting a brain tumor neoantigen, opening the door for further investigation into cell therapy against this class of antigens.

IMMU-24. IMPROVING OUTCOMES IN OLDER ADULTS WITH GLIOBLASTOMA BY REVERSING AGE-RELATED CHANGES

Erik Ladomersky[1], Lijie Zhai[1], Lakshmi Bollu[1], April Bell[1], Kristen Lauing[1], Rimas Lukas[2], and Derek Wainwright[1]; [1]Northwestern University, Chicago, IL, USA, [2]Northwestern Medicine Lou and Jean Malnati Brain Tumor Institute, Chicago, IL, USA

Wild-type IDH glioblastoma (wtGBM) represents ≥90% of human GBM patient diagnoses with a median age of onset at 68-70 years of age. We previously found a decline of GBM patient survival with progressive age and that subjects ≥65 years of age had the poorest prognosis. We also showed an age-dependent enhancement of immune suppression in the brain that negatively affected immunotherapeutic efficacy in older adult mice with syngeneic brain tumors. Here, we extended those observations while studying C57BL/6 mice with intracranial CT-2A or GL261 between 80-110 weeks old - analogous to the age of a wtIDH GBM patient diagnosis. Overall survival of older adult mice with CT-2A or GL261 was significantly decreased when subjects were lymphopenic for $CD4^+$ T cells as compared to an IgG Ab treatment group (n=12/group; $p< 0.01$). $CD8^+$ T cell or NK cell leukopenia had no effect on survival outcomes. The negative effect of $CD4^+$ T cell lymphopenia in older adults was not observed in younger mice with brain tumors. We also investigated the increased immunosuppression in the brain and its relationship to the accumulation of senescent cells and the treatment with standard of care radiation/temozolomide (RT/TMZ). p16INK4A, a marker for senescent cells, was increased in non-tumor cells of the brain during advanced age and its expression was increased after treatment with RT/TMZ. Older adult mice with brain tumors and treated with senolytics showed decreased p16INK4A levels after treatment with RT/TMZ. Senolytic treatment also improved the efficacy of combination therapy with RT, anti-PD-1 mAb, and IDO enzyme inhibitor in older adults as compared to senolytics alone or the triple immunotherapeutic cocktail alone (n=12-15/group; $p< 0.01$). Collectively, the results suggest that strategies aimed at reversing the effects of the aging combined with tumor eradication therapies may be particularly beneficial for older adult human patients with GBM.

IMMU-25. SYNERGY BETWEEN TMZ AND INDIVIDUALIZED MULTIMODAL IMMUNOTHERAPY TO IMPROVE OS OF IDH1 WILD TYPE MGMT PROMOTOR UNMETHYLATED GBM PATIENTS

Stefaan Van Gool, Jennifer Makalowski, Volker Schirrmacher, and Wilfried Stuecker; IOZK, Köln, Germany

The prognosis of IDH1 wild type MGMT promotor unmethylated (MGMT-p-UM) GBM patients remains poor. Addition of TMZ to radiotherapy shifted the median OS from 11.8 to 12.6 months (Stupp, Lancet Oncol 2019). We retrospectively analysed the value of individualized multimodal immunotherapy (IMI) to improve OS in these patients. Adults with first event of IDH1wt GBM and documented status of MGMT-p-UM, and treated with IMI in the period June 2015 till July 2020, were selected. IMI consisted of 1/ immunogenic cell death (ICD) therapy (NDV injections + modulated electrohyperthermia), 2/ active specific immunotherapy with autologous mature dendritic cells loaded with tumor lysate or ICD therapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies (IO-Vac® is an approved advanced therapy medicinal product since 27/05/2015), 3/ modulatory immunotherapy adapted to the patient, and 4/ complementary medicines. Twenty-eight patients (11f, 17m) had a median age of 48y (range 18-69) and a KPI of 90 (50-100). Extent of resection was complete (11), < complete (9) or not documented (8). Seven patients were treated with surgery/radio(chemo)therapy and subsequent IMI (Group-1); 21 patients were treated with radiochemotherapy followed by maintenance TMZ + ICD therapy, followed by DC vaccines (Group-2). Both groups received further maintenance ICD therapy. Age, KPI and extent of resection were not different amongst both groups. PFS was not assessed because of challenges about pseudoprogression. The median OS of group-1 patients was 11m (2y OS: 0%). Surprisingly the median OS of group-2 patients was 18m with 2y OS of 17% (CI95%: +31, -15), which was significantly (Log-rank: p = 0.027) different from group-1. The data suggest that addition of IMI after local therapy on its own has no relevant effect on OS in IDH1 wild type MGMT-p-UM GBM patients, similar to maintenance TMZ. However, the combination of both TMZ + IMI significantly improves median OS.

IMMU-26. SAFETY AND EFFICACY OF PVSRIPO IN RECURRENT GLIOBLASTOMA: LONG-TERM FOLLOW-UP AND INITIAL MULTICENTER RESULTS

Annick Desjardins[1], Matthias Gromeier[2], Henry Friedman[2], Daniel Landi[1], Allan Friedman[3], David M Ashley[4], William Curry[5], Nicholas Butowski[6], Andrew Sloan[7], Patrick Wen[8], Robert Cavaliere[9], Elizabeth Gerstner[10], Mitchel Berger[11], Robin Buerki[12], E. Antonio Chiocca[13], Eric Sauvageau[14], Andrea Kelly[15], W. Garrett Nichols[15], Lori Mixson[15], Adam Dickinson[15], Kristin Orr[15], Chris Learn[15], and Darell Bigner[16]; [1]Preston Robert Tisch Brain Tumor Center at Duke, Durham, NC, USA, [2]Duke University, Durham, NC, USA, [3]Duke University Health System, Durham, NC, USA, [4]Duke University, Raleigh, NC, USA, [5]Mass General Cancer Center, Boston, MA, USA, [6]University of California, San Francisco, San Francisco, CA, USA, [7]UH Cleveland Medical Center & Seidman Cancer Center, Cleveland, OH, USA, [8]Harvard Medical School, Boston, MA, USA, [9]Baptist MD Anderson Cancer Center, Jacksonville, FL, USA, [10]Massachusetts General Hospital, Boston, MA, USA, [11]School of Medicine, University of California San Francisco, San Francisco, CA, USA, [12]University Hospitals Cleveland Medical Center & Seidman Cancer Center, Cleveland, OH, USA, [13]Harvey Cushing Neuro-oncology Laboratories, Department of Neurosurgery, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA, Boston, MA, USA, [14]Lyerly Neurosurgery, Jacksonville, FL, USA, [15]Istari Oncology, Inc., Morrisville, NC, USA, [16]Duke University School of Medicine, Durham, NC, USA

BACKGROUND: Recurrent glioblastoma (rGBM) is rapidly fatal (median overall survival [mOS] of ~9 months; OS at 12 months [OS12] < 35%) with approved therapies (lomustine±bevacizumab). PVSRIPO is an intratumoral immunotherapy targeting CD155 on antigen-presenting and malignant cells of solid tumors. Preclinically, PVSRIPO delivers a systemic, tumor antigen-specific, polyfunctional T-cell mediated anti-tumor response. Interim, single-center, phase (Ph) 1 results showed greater long-term survival with PVSRIPO vs. criteria-matched external control rGBM patients (Desjardins 2018). Updates to Ph1 safety (at the Ph2 dose) and efficacy and interim multicenter (Ph2) results are presented. METHODS: Adults with histologically-confirmed rGBM, Karnofsky performance status ≥ 70, and an active, supratentorial, contrast-enhancing lesion (1-5.5cm) received PVSRIPO ($5x10^7$ $TCID_{50}$) intratumorally via convection-enhanced delivery on Day 1, with a planned follow-up of 24 months. Safety (treatment-emergent adverse events [TEAEs]), efficacy (reported as OS12, OS24, mOS), and blood/tissue were assessed. RESULTS: 149 patients (>90% with 1-2 prior progressions, including failure of SOC and patients with prior bevacizumab failure) received the Ph2 dose of PVSRIPO (n=30 received other doses in Ph1 with safety summarized previously). Follow-up durations for surviving patients were 51-74 months (Ph1) and 10-44 months (Ph2). No dose-limiting toxicities occurred; up to 97% of patients experienced mostly grade 1-2 related TEAEs; ≤ 23% patients experienced grade ≥ 3 related events. Neurologic symptoms related to peritumoral edema were most common (> 90% patients) and were effectively managed with low-dose bevacizumab/corticosteroids. Survival estimates were: OS12: 54%, 50%; OS24: 18%, 17%; mOS: 12.3 (95% CI 10,15.3), 12 (10.6,13.7) months, for the Ph1 and Ph2 trials, respectively. Baseline correlates of longer survival included smaller lesions and methylated MGMT-promoter status. CONCLUSIONS: The multicenter/Ph2 study replicated the single-center/Ph1 results. Relative to published data with approved therapies, PVSRIPO was associated with greater long-term survival and mOS in patients with rGBM and was generally well-tolerated.

IMMU-27. LONG TERM STABILIZATION OF RECURRENT HIGH-GRADE GLIOMA WITH PD-1 INHIBITOR PEMBROLIZUMAB IN TWO CASES

Matthew Moldenhauer[1], Steven Du[2], Dan Fu[3], Joon Myung[3], Daniela Bota[1], and Xiao-Tang Kong[3]; [1]University of California, Irvine, Irvine, CA, USA, [2]University of Southern California, Los Angeles, CA, USA, [3]University of California, Irvine, Orange, CA, USA

INTRODUCTION: Despite PD-1 inhibition having success in many cancers, it has uncertain effects in brain tumors. We report two cases of recurrent high-grade gliomas that have remained stable for over one year since starting pembrolizumab. CASE REPORTS: Case 1: A 59-year-old male was diagnosed with glioblastoma (GBM) without MGMT methylation or IDH mutation in late 2018 after surgery. He received radiation and temozolomide (TMZ) followed by adjuvant TMZ before tumor progression. He underwent second tumor debulking with recurrent GBM on pathology with negative PD-L1 expression. He started carboplatin. Progression was noticed after 7 to 8 cycles. Pembrolizumab was added. Tumor was stabilized. Carboplatin was completed after total 12 cycles and the patient has continued single agent of

pembrolizumab for more than one year with stable brain MRIs. The patient has survived for 24 months since recurrence and 30 months since diagnosis. Case 2: A 53-year-old male had a brain tumor discovered on MRI in 2012 and received no treatment until resection in 2014. In 2016, he underwent second tumor debulking and was diagnosed with anaplastic oligodendroglioma with negative PD-L1 expression. He received radiation followed by PCV regimen. 17 months since diagnosis, he had first tumor progression on PCV. TMZ was started. 22 months since diagnosis, bevacizumab was initiated due to further growth. 33 months since diagnosis, pembrolizumab was added due to new lesions after 12-months of bevacizumab therapy. His tumor was stabilized. Bevacizumab was eventually discontinued. He has continued single agent pembrolizumab for 6 months so far. His tumor has been stable for 22 months since starting pembrolizumab. Survival has been 38 months from first recurrence and 7 years since tissue diagnosis. DISCUSSION: These cases demonstrate the potential effects of anti-PD-1 immunotherapy in stabilizing recurrent high-grade glioma with combination of other treatment agents followed by single agent as maintenance therapy.

IMMU-28. DECONVOLUTION OF SPATIALLY RESOLVED T CELL RECEPTOR PROFILING (SPTCR-SEQ) UNCOVERED REGIONAL ANTI-TUMOR IMMUNITY IN GLIOBLASTOMA

Jasim Kada Benotmane[1], Jan Kückelhaus[1], Kevin Joseph[2], Jürgen Beck[2], Oliver Schnell[2], Vidyha Ravi[2], and Dieter Henrik Heiland[2]; [1]Clinic for Neurosurgery, University Clinic Freiburg, Freiburg, Baden-Wurttemberg, Germany, [2]University Clinic of Freiburg, Freiburg, Baden-Wurttemberg, Germany

The diversity to T cell responses and clonality in spatially heterogeneous glioblastoma is of paramount importance to explore underlying mechanisms of anti-tumor immunity. Spatial transcriptomics, a novel technology to map the transcriptional architecture, is technically limited to discover T cell receptor (TCR) sequences as the 3' approach lacks sufficient coverage. Here, we established SPTCR-seq, a method to capture TCR sequences followed by long-read sequencing to enable full-length TCR reconstruction. We performed 10X Visium spatial transcriptomics on 9 primary and recurrent glioblastoma with both 3'-sequencing and SPTCR-seq. For SPTCR-seq, we target enriched T cell receptor sequences by capturing by hybridization followed by Oxford-Nanopore long-read sequencing. The on-target rate was above 80% for captured TCR genes and spatial barcode was successfully aligned in more than 60%. IgBlast and MixCR were used to reconstruct the TCR and map T cell clonality. Within our recent developed spatial transcriptomic analysis framework (SPATA2), we build a novel toolbox, SPATA-Immunology, which enables integration of stRNA-sequencing data and spatially resolved TCR sequencing. Our data showed that clonal evolution of T cells is limited to regional areas underpinned by significant spatial autocorrelation coefficient (0.6-0.95, padj< 0.001). In the surrounding tumor cell spots, the recently described transcriptional program "reactive immune" (RI), was significantly enriched. Using spotlight, a computational approach to project scRNA-sequencing into the spatial space, we found a local enrichment of CD163 positive macrophages exclusively in areas of large T cell clonality. Imaging mass cytometry of a consecutive section confirmed the spatial confluence of T-cell infiltration and CD163-positive macrophages. Through DeepTCR we uncovered potential epitopes which correlate with T cell clonality and might help to discover novel targets for CART therapy. Spatial profiling of TCR sequences through SPTCR-seq is a powerful tool to investigate anti-tumor immunity in glioblastoma and allows to discover general and personalized targets for immunotherapy.

IMMU-29. B-CELL-BASED VACCINE PRODUCES GLIOBLASTOMA-REACTIVE ANTIBODIES THAT CONTRIBUTE TO TUMOR CLEARANCE

Brandyn Castro[1], Mark Dapash[2], David Hou[3], Aida Rashidi[3], Deepak Kanojia[1], Peng Zhang[3], Aurora Lopez-Rosas[3], Yu Han[3], Irina Balyasnikova[1], Roger Stupp[1], Jason Miska[3], Maciej Lesniak[1], and Catalina Chang[1]; [1]Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [2]University of Chicago, Chicago, USA, [3]Northwestern University, Chicago, USA

Glioblastomas (GBM) are characterized by a strong immunosuppressive environment, contributing to their poor prognosis and limited therapeutic response to immunotherapies. B-cells represent a unique opportunity to promote immunotherapy due to their potential to kill tumors by both cellular and humoral immunity. To generate our B-cell-based vaccine (B_{Vax}) platform, we activated 41BBL$^+$ B cells from tumor bearing mice or GBM patient blood with BAFF, CD40, and IFNg. We have previously demonstrated that B_{Vax} potentiates radiation therapy, temozolomide and checkpoint blockade in murine models of GBM via enhancement of CD8$^+$ T-cell based immunity. The aim of this current study is to evaluate the humoral effector functions of B_{Vax}. We examined the antibody (Ab) repertoire *in vivo* from serum of tumor-bearing B-cell knockout mice treated with B_{Vax} or by *ex vivo* stimulation of patient-derived B_{Vax}. Upon systemic administration, B_{Vax} infiltrates the tumor where it differentiates into plasmablasts. Murine B_{Vax}- and B_{Naive}-derived serum immunoglobulin generated *in vivo* showed that the majority of murine B_{Vax}-derived Ab were IgG isotype, while B_{Naive} mainly produced IgM isotype. Transfer of IgG from B_{Vax} treated mice directly into tumors of recipient animals significantly prolonged their survival, demonstrating anti-tumor cytotoxicity directly through humoral immunity. Patient-derived B_{Vax} activated *ex vivo* showed a plasmablast phenotype and the Ab repertoire supports the previous findings seen in our murine model. Our work suggests B_{Vax}-derived IgGs role in antibody-dependent cellular cytotoxicity and improved survival in murine models. This function, in addition to its role in cellular immunity against GBM, renders B_{Vax} a potentially effective alternative immunotherapeutic option for GBM patients.