SPCR-02

NEUROCOGNITIVE FUNCTION IN PATIENTS WITH LEPTOMENINGEAL METASTASIS TREATED WITH PROTON CRANIOSPINAL IRRADIATION

Denise Correa, Adrian Koch, Raymond Baser, Elena Pentsova, Suzanne Wolden, Brandon Imber, Adrienne Boire, Jonathan Yang; Memorial Sloan Kettering Cancer Center, New York, NY, USA

BACKGROUND: Proton craniospinal irradiation (pCSI) as a potential treatment for patients with solid tumor leptomeningeal metastasis (LM) is being assessed in a phase II randomized study comparing it with photon involved-field radiotherapy (RT). We report the preliminary results of prospective neurocognitive function in a subset of patients treated with pCSI. METHODS: Patients with LM and without evidence of CNS disease progression completed standardized neurocognitive tests of attention and working memory, executive function, and verbal memory at baseline (pre-pCSI), and 3 and 6 months post-pCSI. All patients received chemotherapy (baseline and follow up) and memantine (follow up). Means across the three timepoints were estimated for each neurocognitive test score using a linear mixed model (LMM) predicting the score by timepoint. Mean changes between pairs of timepoints were similarly estimated from the LMMs and tested for statistical significance using model-based contrasts. RESULTS: Baseline, 3-month and 6-month neurocognitive data were available for 12, 11, and 8 patients, respectively. Linear mixed model analyses showed a significant decline in graphomotor speed (Trails A, p=0.03), verbal learning (HVLT-R Total Learning, p<0.001), and verbal recognition memory (HVLT-R Discrimination, p=0.03) from baseline to 3 months post-pCSI, with scores remaining stable at 6 months post-pCSI. There was a significant decline in timed set-shifting (Trails B, p=0.04) from baseline to 6 months post-pCSI. There were no significant changes in attention and working memory over the follow-up period. CONCLUSION: Preliminary results in a subset of patients showed a decline in graphomotor speed and verbal memory at 3 months and executive function at 6 months post-pCSI, possibly related to the early adverse effects of RT. These results are overall consistent with findings in other populations treated with whole-brain RT. However, there was no change in attention and working memory and most cognitive domains remained stable at six months with pCSI.

SPCR-03

NEUROCOGNITIVE OUTCOMES FROM PHASE 1 TRIAL OF BMX-001 IN COMBINATION WITH CONCURRENT RADIATION THERAPY AND TEMOZOLOMIDE IN NEWLY DIAGNOSED HIGH-GRADE GLIOMA PATIENTS

Katherine Peters[1], John Kirkpatrick[1], Ines Batinic-Haberle[1], Mary Lou Affronti[1], Sarah Woodring[1], Eric Lipp[1], James Herndon[1], Kendra Boyd[1], Ivan Spasojevic[1], Sara Penchev[2], Shayne Gad[3], David Silberstein[2], Margaret Johnson[1], Annick Desjardins[1], Henry Friedman[1], David Ashley[1], James Crapo[2]; [1]Duke University Medical Center, Durham, NC, USA. [2]BioMimetix JV, LLC, Greenwood Village, CO, USA. [3]Gad Consulting, Durham, NC, USA

INTRODUCTION: Neurocognitive dysfunction can result from radiation therapy which is the mainstay of treatment for high-grade glioma, particularly glioblastoma. Preclinical observations found that BMX-001, a novel metalloporphyrin, acts as a radioprotectant for normal CNS cells yet as a radiosensitizer to cancer cells in human GBM xenograft experiments. In a phase 1 study evaluating the safety of BMX-001 in combination with concurrent radiation therapy and temozolomide, we further studied neurocognitive function before and after concurrent radiation therapy and temozolomide in newly diagnosed high-grade glioma patients. METHODS: We performed a phase 1 study of BMX-001 combined with radiation therapy (6-week total of 59.4-60 Gy) and temozolomide (75 mg/m2/day for 42 days). We administered BMX-001 as a subcutaneous injection at a loading dose before radiation therapy and temozolomide and then subsequent doses twice weekly for eight weeks. A key secondary endpoint was the evaluation of neurocognition. We performed neurocognitive testing with the computerized program CNS Vital Signsâ. This battery consists of seven tests: verbal memory, visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention, and a continuous performance test. We defined neurocognitive impairment at baseline as a z-score ≥ 1.5 SDs below the normative mean. We described improvements or declines in neurocognition at 2 and 6 months from baseline. RESULTS: Fifteen patients (age 19-80 years) enrolled and underwent neurocognitive testing before and after RT. All patients had WHO grade 4 glioblastoma. Most subjects had neurocognitive impairment ranging from 46.7-to 80% on specific neurocognitive tests. At two months (N=15) and six months (N=9), most testing demonstrated improved neurocognitive performance. CONCLUSIONS: Neurocognitive function is maintained and can improve after concurrent radiation therapy and temozolomide in this high-grade glioma cohort treated with BMX-001 during concurrent radiation therapy and temozolomide.

SPCR-04

EFFECTS OF BRAIN METASTASES ON NEUROCOGNITIVE FUNCTION: BASELINE RESULTS OF A LONGITUDINAL TRIAL

Randa Higazy[1,2], Matthew Ramotar[1], Zhihui Amy Liu[3,2], Anna T. Santiago[3], Natalya Kosyak[1], Geoffrey Liu[4,2], Rebecca Simpson[5], David B. Shultz[1,2], Kim Edelstein[5,2]; [1]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [2]University of Toronto, Toronto, ON, Canada. [3]Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [4]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [5]Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

PURPOSE: Neurocognitive dysfunction is common in patients with advanced metastatic cancer. The contribution of brain metastases (BrMets) to neurocognitive outcomes is uncertain. We examined the impact of BrMets on cognitive outcomes before CNS-directed treatment and compared findings to patients with advanced metastatic cancer without BrMets. Here we present results from an ongoing prospective, longitudinal study. METHODS: English-speaking adults followed at the brain metastases and lung cancer clinics underwent neurocognitive testing using a standardized battery (prior to cranial radiotherapy, if applicable), with follow-up assessments 3, 6, 9, 12, 18, and 24 months later. We calculated z-scores and impairment rates for composite neurocognitive function and memory, attention/working memory, processing speed and executive function domains. Impairment was defined according to International Cancer and Cognition Task Force criteria. RESULTS: 78 patients with BrMets (50% female; mean age (SD):61(11) years) and 28 patients with metastatic non-small cell lung cancer (mNSCLC) with no known BrMets (71% female; age 67(9) years) were included. Baseline neurocognitive composite scores were impaired in both groups (BrMets: 61.5%; nonBrMets: 60.7%). Impairment rates varied between groups and across domains (BrMets vs nonBrMets: memory: 35.9%vs25.0%; attention/working memory: 35.8%vs21.4%; processing speed: 10.3%vs7.1%; executive function: 44.0%vs35.7%). Subgroup comparisons between BrMets patients with mNSCLC (N=29) and mNSCLC patients without BrMets, none of whom had targetable mutations, revealed no differences in impairment rates, but BrMets patients had slower processing speed than nonBrMets patients (mean(SD): -0.6(1.4) vs -0.1(1.9); Wilcoxon signed-rank test, p = 0.043). CONCLUSION: Neurocognitive impairment in patients with advanced cancers is common. Our preliminary findings demonstrate no clear difference in cognitive outcomes between patients with BrMets and those with advanced metastatic disease not involving the brain. Our work examining how neurocognitive outcomes evolve over time in patients with and without BrMets, and demographic, disease, and treatment variables associated with those outcomes, is ongoing.

FINAL CATEGORY: SYSTEMIC THERAPEUTICS

SYST-01

MULTI-INSTITUTIONAL RANDOMIZED TRIAL COMPARING CANCER STEM CELL-TARGETED VS PHYSICIAN-CHOICE TREATMENTS IN PATIENTS WITH RECURRENT HIGH-GRADE GLIOMAS (NCT03632135)

Soma Sengupta[1], Tulika Ranjan[2], Alexander Yu[3], Candace Howard[4], Ricky Chen[5], Rekha Chaudahary[1], Nicholas Marko[1], Darit Aregawi[6], Michael Glantz[6], Jon Glass[7], Richard Green[8], Christine Lu-Hemerson[9], Aaaron Mammoser[10], Hugh Moulding[11], Steven Jubelirer[12], Jason Schoroeder[13], Mark Anderson[4], Frances Chow[14], Seth Lirette[4], Krista Denning[15], Anthony Alberico[15], Jagan Valluri[15], Pier Paolo Claudio[16]; [1]University of Cincinnati, Cincinnati, OH, USA. [2]Tampa General Hospital, Tampa, FL, USA. [3]Allegheny Health Network, Pittsburgh, PA, USA. [4]University of Mississippi Medical Center, Jackson, MS, USA. [5]Providence Brain & Spine Institute, Providence, WA, USA. [6]Penn State Neuroscience Institute, Hershey, PA, USA. [7]Thomas Jefferson University, Philadelphia, PA, USA. [8]Southern California Permanente Medical Group, Los Angeles, CA, USA. [9]Maine Medical Center, Scarborough, ME, USA. [10]Louisiana State University, New Orleans/ LA, USA. [11]St. Luke's University Health Network, Bethlehem, PA, USA. [12]Charleston Area Medical Center, Charleston, WV, USA. [13]University of Toledo, Toledo, OH, USA. [14]University of Southern California, Los Angeles, CA, USA. [15]Marshall University, Huntington, WV, USA. [16]University of Mississippi, Jackson, MS, USA

BACKGROUND: Clinical outcomes in patients with recurrent high-grade glioma (HGG) remain poor. Cancer stem cells (CSCs) have been implicated in metastasis, treatment resistance and recurrence of HHGs. We have shown in several clinical studies that anti-CSC-directed therapy provides benefits in many cancer types; however, this is the first report of a randomized clinical

trial evaluating it for recurrent HGGs. OBJECTIVE: Determine whether CSC-targeted cytotoxic agents selected by ChemoID assay-guided therapy improves survival in patients with recurrent HGG. DESIGN, SETTING, AND PARTICIPANTS: In this parallel-group, randomized, phase-3 clinical trial, patients at 13 clinical sites in the USA with grade-III/IV recurrent glioma (2016 WHO guidelines) were randomized 1:1 to either ChemoID assay-guided therapy or physician-choice therapy, and then treated and followed until unacceptable toxic effects, hospice, or death. MAIN OUTCOMES AND MEASURES: The primary endpoint was overall survival (OS). RESULTS. Combined median follow-up was 9 months. Median OS (mOS) was 12.5 months (95% CI, 10.2-14.7) in the ChemoID assay-guided group vs 9 months (95% CI, 4.2-13.8) in the physician-choice group (log-rank P = .010). Risk of death was significantly lower in the ChemoID assay group (HR = 0.44; 95% CI, 0.24-0.81; P = .008). Median progression free survival (PFS) was 10.1 vs 3.5 months (95% CI, 4.8-15.4 vs 1.9-5.1) (HR, 0.25; 95% CI, 0.14-0.44; P < .001). CONCLUSIONS AND RELEVANCE: Primary endpoint was met in this randomized clinical trial. The mOS was 3.5 months longer in the ChemoID assay-guided group vs the physician-choice group.

SYST-02

PHASE ⅡB CLINICAL TRIAL OF NEOADJUVANT CHEMOTHERAPY REVERSING GLIOMA STEM CELLS CHEMORESISTANCE IN NEWLY DIAGNOSED GBM WITH MGMT PROMOTER UNMETHYLATION

Jun Dong, Liping Wang, Yanming Chen; The Second Affiliated Hospital of Soochow University, Suzhou, China

PURPOSE: To evaluate clinical efficacy and safety of combination of nicardipine and valproic acid on temozolomide (TMZ) neoadjuvant chemotherapy targeting on glioma stem cells (GSCs) in newly diagnosed glioblastoma multiforme (GBM) patients with O^6-methylguanine-DNA-methyltransferase (MGMT) promoter unmethylation. METHODS: From June 2018 to April 2021, newly diagnosed GBM patients after tumor surgical removal and concurrent radio-chemotherapy with TMZ, with MGMT promoter unmethylation were randomly assigned to two groups. The control group was applied standard TMZ regimen. The trial group was administered standard TMZ regimen, plus nicardipine(20mg/d) and valproic acid (1.2g/d) as neoadjuvant treatment against GSCs chemoresistance. The relevant treatment data and adverse reactions of the patients were collected, Karnofsky performance status (KPS) score, progression-free survival (PFS) and overall survival (OS) were evaluated during patient follow-up. RESULTS: 33 patients were enrolled in this study, eighteen patients were randomly assigned in the trial group and 15 patients were in the control group. There was no statistical difference in gender composition, age, degree of surgical resection, or KPS score before treatment between the two groups. The median progression-free survival (mPFS) in the trial group was 10.8 months (95%*CI* 5.81-15.79 month), and the mPFS in the control group was 7.1 months (95%*CI* 5.12-9.08 month), which was a statistically difference (Log-Rank test P=0.033). The median overall survival (mOS) increased from 12.1 months (95%*CI* 9.18-15.00 month) in the control group to 15.7 months (95%*CI* 7.67-23.73 month) in the trial group (Log-Rank test *P*=0.015). There was no statistically significant difference in the incidence of adverse reactions between the two groups, and there were no treatment regimen related deaths. CONCLUSIONS: TMZ combined with neoadjuvant of nicardipine and valproic acid against GSCs chemoresistance can prolong the survival time of patients who was newly diagnosed glioblastoma with MGMT promoter unmethylation. The preferred regimen can be applied safely without serious adverse events, which deserved further multi-center clinical investigations.

SYST-03

INCIDENCE AND SURVIVAL OF PATIENTS WITH INTRACRANIAL METASTATIC DISEASE AND ERBB2-POSITIVE GASTROINTESTINAL CANCERS: A RETROSPECTIVE COHORT STUDY

Madison Sherman[1,2], Anders W. Erickson[3], Sunit Das[4,5]; [1]University of Waterloo, Waterloo, ON, Canada. [2]Division of Neurosurgery, St. Michael's Hospital, Toronto, ON, Canada. [3]Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [4]Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [5]Division of Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

BACKGROUND: Intracranial metastatic disease (IMD) is a mortality-driving complication of gastrointestinal (GI) cancers. In breast cancer, ERBB2 positivity is associated with shorter overall survival (OS) and increased risk of IMD, and while ERBB2 status is relevant in primary GI cancer, no study has directly assessed the relationship of ERBB2 status and IMD in these patients. METHODS: Records for adult patients with GI cancer and IMD, treated with ERBB2-therapy between 2005 and 2018 were retrieved from ICES. Baseline characteristics were compared between subcohorts stratified by IMD and ERBB2 statuses. Kaplan-Meier and Cox regression analyses were performed to estimate survival. RESULTS: Records for 99,256 patients with GI cancer were collected, and IMD was diagnosed in 2002 patients. The highest IMD incidence rate was among patients with esophageal cancer (5.5%). Among patients with ERBB2+ disease, 306 had gastric (9 IMD), 168 esophageal (15 IMD), and 17 colorectal cancer. Diagnosis of IMD was associated with shorter OS among patients with colorectal (HR 3.0; 95% CI 2.9–3.2), gastric (HR 1.7; 95% CI, 1.5–1.9), and esophageal cancers (HR 1.2; 95% CI, 1.1–1.4). Post-IMD ERBB2-targeted therapy was not associated with OS among patients with ERBB2+ esophageal (HR 0.5; 95% CI, 0.2–1.2; n = 15) or gastric cancer (HR 0; 95% CI 0–Inf; n = 9). CONCLUSION: Our study assessed patients with ERBB2+ GI cancer and IMD. Diagnosis of IMD was associated with shorter survival in gastric, esophageal, and colorectal cancers. Post-IMD ERBB2 therapy was not associated with OS, and IMD diagnosis was associated with prolonged survival in patients with stage 4 ERBB2+ disease, although interpretation of these results is complicated by small sample size and selection bias. Our results motivate increased reporting and inclusion of patients with ERBB2+ GI cancers in clinical trials.

SYST-04

PRELIMINARY REPORT OF A CLINICAL TRIAL EVALUATING THE SAFETY AND EFFICIENCY OF NEOADJUVANT CAMRELIZUMAB AND APATINIB IN PATIENTS WITH RECURRENT HIGH-GRADE GLIOMAS: A PROSPECTIVE, PHASE II, SINGLE-ARM STUDY

Fuhua Lin, Chengcheng Guo, Qunying Yang, Yinsheng Chen, Chao Ke, Ke Sai, Ji Zhang, Xiaobing Jiang, Wanming Hu, Shaoyan Xi, Jian Zhou, Depei Li, Zhihuan Zhou, Qinqin Zhao, Xi Cao, Zhongping Chen; Sun Yat-sen University Cancer Center, Guangzhou, China

High-grade glioma is the most common malignant primary brain tumor in the central nervous system. Multiple strategies such as surgery, radiotherapy, and chemotherapy have been used, but the prognosis of patients with high-grade glioma remains poor. No standard treatment exists for recurrent gliomas; however, combination therapies of programmed cell death protein 1 blockades with antiangiogenic agents have demonstrated promising effects in different solid tumors. We have initiated a clinical trial designed to evaluate the safety and efficiency of neoadjuvant therapy using camrelizumab and apatinib in patients with recurrent highgrade gliomas. In this prospective, Phase II, singlearm study, patients with recurrent highgrade gliomas will receive singledose intravenous injection of camrelizumab (200 mg) and daily oral administration of apatinib (250 mg/day for 7 days) 14 days before surgery for recurrent tumor. Sequential therapy will begin 2 weeks after surgery with the biweekly injection of camrelizumab and 4 weeks after surgery with the daily administration of apatinib. Treatment of camrelizumab and apatinib will be continued until disease progression or unacceptable toxicity or death. The trial is planned to enroll 30 patients. Up-to date (March 31, 2022), 12 patients had been enrolled, in which, 9 were GBM. Three patients died, while 4 cases on trial more than 6 months, the longest already 1 year. Although an evaluation is still impossible to be conducted yet, some patients have shown a promising outcome. We will present updated results on the meeting. These preliminary data suggest that this study would be worthwhile. This study was approved by the Ethics Committee of Sun Yatsen University Cancer Center (Guangzhou, China; approval No. SLB202014901). This study was registered with ClinicalTrials.gov under identifier NCT04588987.

SYST-05

OPTIMIZING HER2-TARGETED THERAPIES (TT) FOR BREAST CANCER (BC) LEPTOMENINGEAL METASTASES (LM): A SYSTEMATIC REVIEW AND META-ANALYSIS

Anna-Maria Lazaratos[1,2], Sarah Maritan[1,3], Andrea Quaiattini[4], Nathaniel Bouganim[5,6], Matthew Dankner[1,3]; [1]Rosalind and Morris Goodman Cancer Institute, Montreal, QC, Canada. [2]Faculté de Médecine, Université de Montréal, Montreal, QC, Canada. [3]Department of Medicine, Division of Experimental Medicine, McGill University, Montreal, QC, Canada. [4]McGill University Library Sciences, Montreal, QC, Canada. [5]Gerald Bronfman Department of Oncology, Faculty of Medicine and Health Sciences, Montreal, QC, Canada. [6]Cedars Cancer Centre, McGill University Health Centre, Montreal, QC, Canada

INTRODUCTION: LM is a debilitating condition associated with metastatic cancers, including BC. When oncogenic drivers are identified, TT represents an appealing therapeutic strategy. However, the efficacy of TT for LM is unknown as LM patients are routinely omitted from clinical trials. METHODS: We conducted a systematic review and meta-analysis of individual patient data to evaluate the effectiveness of HER2-TT in HER2+ BCLM in accordance with PRISMA guidelines. TTs evaluated included trastuzumab (intrathecal (IT) or intravenous (IV)), trastuzumab-