Title

NCOG-44. NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE IN A PHASE II STUDY OF PEMBROLIZUMAB OR PEMBROLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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INTRODUCTION: Gliomas are one of the most common central nervous system tumors in adults. The Response Assessment Criteria in Neuro-Oncology (RANO) was developed to standardize the radiographic parameters used to assess therapeutic outcomes in glioma patients. A previous study has shown an association between therapeutic response based on RANO criteria and overall survival in glioma patients. However, the feasibility of applying RANO criteria in settings with limited resources has never been reported. This study aims to assess the feasibility of applying RANO criteria in clinical settings in Indonesia. This study also wants to see the role of the RANO criteria as a prognostic factor for gliomas in Indonesia. METHOD: Data of glioma patients were retrospectively collected from Dharmais Cancer Hospital in Jakarta, Indonesia. Dharmais Cancer Hospital is the highest referral hospital for brain tumors in the country. Clinical and demographic data were collected from the medical record. RESULTS: From 138 identified glioma patients from 2017 to May 2020, only 34 patients can be assessed using RANO criteria. The majority of the patients do not have post-surgical MRI that can be used as a baseline. Among 34 included patients, 38.2% were categorized as responsive, 23.5% as stable disease and 38.2% were categorized as progressive. Kaplan-Meier analysis showed that the median overall survival in the progressive group is significantly shorter than the median survival of responsive/stable group (21.2 vs. 57.5 months respectively, p=0.001). Multivariate cox regression analysis was performed to see the association of RANO criteria and other confounding variables (sex, age, glioma grade, glioma location, and therapy) with overall survival. The result showed that RANO progression was significantly associated with decreased survival (HR 18.38, p=0.045). CONCLUSION: This retrospective analysis demonstrates the feasibility of applying RANO criteria in Indonesia and its association with overall survival.

NCOG-41. FUNCTIONAL OUTCOME FOLLOWING NON-DOMINANT HEMISPHERIC GLIOMA SURGERY FROM THE ASPECT OF INDEPENDENCE LEVEL, COGNITIVE FUNCTION AND RETURN TO SOCIAL LIVES

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BACKGROUND: Functional outcome has been paid much attention in surgery for eloquent area or dominant hemisphere. Little is known about functional outcome following surgery for non-dominant hemispheric gliomas, although some resent reports revealed the importance of right cerebral hemisphere on glioma surgery. Here, we investigated functional outcome of right cerebral hemispheric gliomas from the aspect of independence level, cognitive function, and return to social lives. METHODS: Totally 82 patients with right cerebral hemispheric gliomas who underwent surgery for resection in Kanazawa university hospital were studied. Patients were divided into two groups, WHO grade II/III and IV. Karnofsky Performance Status (KPS), Mini-mental state examination (MMSE), and whether or not to return to work at pre-operation and chronic phase were evaluated. To reveal responsible region for decline of each index, the voxel-based lesion symptom (VLSM) analyses were performed. RESULTS: MMSE; no difference was found through postoperative course in grade II/III, whereas postoperative score of grade IV was declined significantly compared with pre-operation (25.1 and 21.9 point; p=0.048). KPS; preoperative independence level was maintained until chronic phase in grade II/III (94.7 and 89.5). While, in grade IV, postoperative KPS was declined significantly than that of pre-operation (82.0 and 70.0, p=0.007). Results of the VLSM analysis revealed that patients who resected temporo-parietal junction in grade IV showed significantly low KPS score. Return to social lives; Reintegration ratio of working population was 71% and 35% for grade II/III and IV, respectively. Of these, as for grade II/III gliomas, the cingulate cortex and medial orbito-frontal cortex relate to return to social lives. CONCLUSIONS: Functional outcome following surgery depends on tumor grade and resected region in right cerebral hemispheric gliomas.

NCOG-42. INITIAL PRESENTATION AND OUTPATIENT VISIT COMPLIANCE OF INMATES WITH BRAIN TUMORS

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INTRODUCTION: While advocacy for inmates with cancer has recently gained momentum, little is known about management of brain tumors in inmates. Delays in acknowledging or recognizing nonspecific initial symptoms can lead to delayed diagnosis and treatment. Inmates with cancer are reported to either be ignored or receive substandard care due in part to cost or logistics (American Civil Liberties Union; ASCO Post 2018). METHODS: In this retrospective study, we identified inmates with gliomas seen in the Ohio State University Neuro-oncology Center between 1/1/2010-4/20/2019. RESULTS: Twelve patients were identified. Median age at presentation was 39.5 years (range 28-62). Eleven patients were Caucasian and one was African American. Diagnoses included glioblastoma (GBM) (n=6), anaplastic astrocytoma (n=1), anaplastic oligodendroglioma (n=1), low-grade astrocytoma (n=3) and anaplastic pleomorphic xanthroastrocytoma (n=1). Patients were more likely to present early after seizures or focal neurologic deficits (9/12) than after headaches alone. Patients with GBM started RT 12-71 days after surgery (median 34.5). One patient's post-RT MRI was delayed by a month and another with GBM had treatment held after 4 cycles of adjuvant temozolomide (TMZ) due to "incarceration issues". For one patient who received adjuvant TMZ, the facility failed to communicate with the primary team throughout treatment. Two patients suffered significant nausea while on chemotherapy due to inability to obtain ondansetron in prison, or due to wrong timing. 7/12 (58%) patients were lost to follow-up for periods of 3-15 months during treatment. Three patients refused adjuvant treatment. CONCLUSIONS: Although this is a small series, our results highlight the inequities and challenges faced by inmates with gliomas who are more likely to forego treatments or whose incarceration prevents them from keeping appropriate treatment and follow-up schedules. Additional studies are needed to define and address these deficiencies in the care of inmates with brain tumors and other cancers.

NCOG-43. NEUROCOGNITIVE IMPAIRMENT AND FRAILTY IN GERIATRIC PATIENTS WITH HIGH GRADE GLIOMA AND THORACIC MALIGNANCY

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BACKGROUND: The median age at diagnosis for high grade glioma is 64 years. With peak incidence 75-84, malignant glial tumors are frequently a disease of the elderly. Common assessment measures fail to accurately gauge geriatric cancer patient fitness. Comprehensive Geriatric Assessment (CGA) is recommended in patients older than 65 to gauge risk of toxicity and tolerance of therapeutic intervention. We reviewed data for older patients with high grade glioma (HGG) and thoracic malignancy (TM) who underwent CGA via Senior Oncology Clinic (SOC) at Levine Cancer Institute. METHODS: From 2015 to 2019 104 thoracic malignancy patients and 19 high grade glioma patients completed CGA via SOC before treatment or a required change in therapy. Data was incorporated into the LCI Senior Oncology Database by the REDCap secure web application, allowing for both quantitative and qualitative data analysis. RESULTS: The median age was 77 in the HGG cohort compared to 80 years with TM. The physician rated Karnofsky Performance Status (KPS) for HGG and TM were similar (76% v 79%) as were the percentages of patients that were frail or prefrail (90% v 87%). Montreal Cognitive Assessment scores were lower in HGG (20 v 23). Considerably more HGG had falls in the 6 months before their assessment (58% v 30%) and gait speed was slower (0.76 m/s v 0.85 m/s). CONCLUSIONS: Older patients with high grade gliomas compared to similar thoracic malignancies had more neurocognitive impairment, falls in the preceding 6 months, and slower gait speed. Physician rated KPS and frailty were similar in both groups. The results illustrate the limitations of physician-rated performance measures and highlight the importance of CGA in older brain tumor patients.

NCOG-44. NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE IN A PHASE II STUDY OF PEMBROLIZUMAB OR PEMBROLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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PURPOSE: The neurologic assessment in neuro-oncology (NANO) scale was developed as a standardized metric to objectively measure neurologic function in brain tumor patients to complement radiographic assessment in defining overall outcome. A multicenter, phase 2 study of pembrolizumab with or without bevacizumab in patients with recurrent glioblastoma incorporated the NANO scale as an exploratory endpoint. METHODS: Neurologic examination was evaluated at baseline and MRI assessments using the NANO scale until patients came off study. Statistical descriptive data analysis was performed using R (version 3.4.3). Correlation analysis utilized Fisher's exact test. RESULTS: NANO compliance rate was 94% in 80 patients accrued on the study. Of the 80 patients, 7 were missing NANO at baseline visit and were excluded from analysis for NANO response criteria. Fifteen patients did not have end of treatment NANO evaluation. Of 73 patients, 35 (48%) had a normal neurologic examination at baseline by NANO. Strength and language accounted for the majority of changes in neurologic function over the course of study treatment. Eighteen patients (25%) had neurologic progression by NANO, of whom 2 did not have concurrent radiographic progression. Three patients (pembrolizumab plus bevacizumab cohort) had a neurologic response associated with stable disease on MRI. NANO assessment prior to initiation of cycle 3 correlated with RANO response (p=0.011), change in KPS (p=0.002) and dexamethasone requirement (p=0.007) while those with NANO progression at this assessment had worse overall survival (291 vs 324 days), but this trend did not achieve statistical significance (p=0.2). CONCLUSIONS: Evaluation of neurologic function by NANO scale was feasible in a multicenter prospective study in patients with GBM with a high compliance rate. The NANO scale objectively tracked stable neurologic function in most patients throughout the trial period and was associated with a trend for survival.

NCOG-45. FIRST-LINE ANTIEPILEPTIC DRUG TREATMENT IN GLIOMA PATIENTS WITH EPILEPSY: LEVETIRACETAM VERSUS VALPROIC ACID

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BACKGROUND: Levetiracetam and valproic acid are two of the most commonly prescribed antiepileptic drugs (AEDs) in patients with a glioma and epilepsy. This study aimed at estimating the cumulative incidence of treatment failure of first-line monotherapy levetiracetam versus valproic acid in glioma patients with epilepsy. METHODS: In this retrospective observational study, a competing risk model was used to estimate the cumulative incidence of treatment failure, from AED treatment initiation, for the two AEDs with death as competing event. Patients were matched on baseline covariates potentially related to treatment assignment and/or outcomes of interest according to the nearest neighbour propensity score matching technique. Secondary outcomes were the cumulative incidence of recurrent seizure, from AED treatment initiation (estimated with a competing risk model), and severity of adverse effects. Maximum duration of follow-up was 36 months. RESULTS: In total, 776 patients using levetiracetam and 659 using valproic were identified. Matching resulted in two equal groups of 429 patients, with similar covariate distribution. The cumulative incidence of treatment failure (any reason) at 12 months for levetiracetam and valproic acid was equal to 33% (95%CI=29-38%) versus 50% (95%CI=45-55%), respectively (p< 0.001). The cumulative incidence of treatment failure due to uncontrolled seizures was significantly lower for levetiracetam compared to valproic acid (12 months: 16% [95%CI=12-19%] versus 28% [95%CI=23-32%]; p< 0.001), but no differences were found for treatment failure due to adverse effects (12 months: 14% [95%CI=11-18%] versus 15% [95%CI=11-18%]; p=0.636). The cumulative incidence of recurrent seizure of levetiracetam was significantly lower compared to valproic acid (12 months: 54% [95%CI=49-59%] versus 67% [95%CI=62-71%]; p< 0.001). No significant differences were found for level of toxicity. CONCLUSION: Our results suggest that levetiracetam has superior efficacy compared to valproic acid, while showing a similar level of toxicity. Therefore, levetiracetam seems the preferred choice for first-line AED treatment in glioma patients.

NCOG-46. A PILOT STUDY OF GERMLINE CODING MUTATIONS ASSOCIATED WITH IMPAIRED DEVELOPMENT AND ADAPTIVE BEHAVIOR IN PEDIATRIC MEDULLOBLASTOMA PATIENTS TREATED ON HEAD START 4

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Children with brain tumors often carry germline mutations that have long been known to contribute to tumorigenesis and treatment response. However, less is known about how germline mutations may impact developmental and behavioral outcomes for children with tumors of the central nervous system (CNS). As the molecular mechanisms governing cancerous and normal tissue expand, we hypothesize that particular germline variants may impact baseline neurocognitive function and/or treatment-induced toxicities. In this preliminary study, 10 children on the Head Start 4 trial diagnosed with medulloblastoma were assessed for baseline adaptive functioning using the Adaptive Behavior Assessment System Third Edition (ABAS-III) and germline whole-exome sequencing was performed. After filtering for high impact variants, Welch's T-tests were used to identify mutations associated with lower ABAS-III General Adaptive Composite (GAC) scores, reflecting developmental and adaptive behavior delays compared with peers their age. We found 20 genes with alterations associated with lower scores with P-values less than 0.05, although none met FDR significance cutoffs. Genes found to be significant included *LAMC1* (P=0.04) and *KRTAP1-1* (P=0.045), which encode members of the laminin and keratin family and are involved in extracellular matrix adhesion. Mutations in *PITX1*, a known suppressor of *RAS*, were also associated with lower ABAS-III GAC scores (P=0.007). We suspect that follow-up studies with more patients will reveal alterations in cell-to-cell communication and signal transduction pathways, as these are common molecular perturbations in tumors that would likely impact regular CNS function. Future research with larger cohorts is essential to validate these findings and to improve our understanding of the functional impact of germline variants on both tumor and regular tissue biology, allowing for a more comprehensive view of the spectrum of neurodevelopmental impairment and novel strategies to circumvent these impairments. Funding: Thrasher Research Fund (JF, AC). R01CA108633, RC2CA148190, U10CA180850(NCI), and OSUCCC (AC).

NCOG-47. CAN YOUNG CHILDREN WITH RELAPSED MEDULLOBLASTOMA BE SALVAGED AFTER INITIAL IRRADIATION-SPARING APPROACHES?

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INTRODUCTION: Irradiation-sparing approaches are used in young children with medulloblastoma (MB) given the vulnerability of the developing brain to neurocognitive impairment. Limited data are available following relapse for these patients. We aimed to describe the management and outcomes of young children with MB who relapsed after initial treatment without craniospinal irradiation (CSI). METHODS: International retrospective study including patients with MB diagnosed between 1995-2017, ≤ 72 months old, initially treated without CSI, who subsequently relapsed. RESULTS: Data are available for 66 patients. The median age at initial diagnosis was 27 months (range, 6-72). At diagnosis, 27 patients had metastatic disease. Initial therapy included conventional chemotherapy or with high-dose chemotherapy (HDC) in 30 and 36 patients, respectively. Eight (12.1%) received upfront focal irradiation. Molecular subgrouping was available for 27 (41%) patients. Ten were SHH, five group 3, six group