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NTOX-04. INVESTIGATION OF N-ACETYLCYSTEINE FOR THE PREVENTION OF CISPLATIN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENTS

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NIMG-100. USEFULNESS OF ^{18}FET-PET FOR CHEMOTHERAPY MONITORING IN NON-CONTRAST ENHANCING GLIOMA

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BACKGROUND: Monitoring treatment response after chemotherapy of gadolinium (Gd) negative gliomas is challenging as conventional MRI often indicates no radiological changes. We hypothesize that molecular imaging using ^{18}F-FET-PET can be used as a biomarker for response assessment in Gd-negative gliomas undergoing chemotherapy. **METHODS:** 61 patients harboring histologically proven Gd-negative WHO grade II (n= 44) or III (n=17) glioma receiving alkylating agents (temozolomide or CCNU/ procarbacine) were included. All patients underwent MRI and ^{18}FET-PET investigations before chemotherapy and 6 months later using a prospective imaging protocol. We calculated T_2-volume, ^{18}FET-PET based biological tumour volume (BTV) and maximal tumour-to-brain ratio (TBR_{max}). A volume decrease >25% of T_2-volume and/or BTV and/or a TBR_{max} reduction of >10% were classified as treatment response, whereas a volume increase >25% and/or a TBR_{max} increase >10% were categorized as tumour progression. Otherwise, stable disease was assumed. Overall survival (OS) and progression free survival (PFS) were calculated from beginning of chemotherapy. Prognostic factors were obtained from proportional hazards models. **RESULTS:** At the time of last follow up, 10 patients died and 42 patients experienced tumour progression. ^{18}FET-PET based assessment of treatment response was significantly associated with both PFS (BTV p=0.004; TBR_{max} p= 0.006) and OS (BTV p<0.001; TBR_{max} = 0.003), while T_2-volume based assessment was not (p=0.84 for PFS and p=0.07 for OS). According to the applied BTV classification scheme, OS was 135.8 months for responders, 92.8 months in case of stable disease, and 40.3 months for non-responders. Lower WHO grade, presence of *IDH1/2* mutation with co-deletion 1p/19q and BTV decrease >25% were independently associated with a prolonged PFS in the multivariate analysis. **CONCLUSION:** ^{18}FET-PET is a promising biomarker candidate for early response assessment in Gd-negative gliomas undergoing chemotherapy. It might be helpful for timely adjustment of a personalized treatment concept and overcomes limitations of conventional structural imaging.

NIMG-101. EVALUATING THE VALIDITY OF EVIDENCE-BASED AANS/CNS GUIDELINES FOR POST-OPERATIVE TIMING OF IMAGING IN PATIENTS WITH NON-FUNCTIONAL PITUITARY ADENOMAS: A PRELIMINARY STUDY IN A COHORT OF PATIENTS

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INTRODUCTION: Non-Functional Pituitary Adenomas (NFPA) are the most common pituitary tumors. Due to lack of hormonal hypersecretion imaging is the main follow-up modality, especially after surgical treatment. Recent evidence-based guidelines recommend the first post-operative MRI be performed no earlier than 3 months to provide the most meaningful information for extend of resection and for cost effectiveness. **METHODS:** We retrospectively reviewed 28 cases of NFPA treated surgically in our institution that were designated to receive their first post-operative imaging at 3 months with the aim to identify factors that led to earlier imaging and whether late imaging was related to unexpected events. **RESULTS:** Twenty-eight patients underwent surgical treatment for NFPA. Twenty-seven underwent transsphenoidal resection and one open craniotomy. Seventeen (60%) were male and 11 (40%) female. Size of tumor ranged from 11mm to 50mm by the largest diameter. MRI of the pituitary gland was performed at or after 3 months post-surgery in all, but 6 patients (21%) who received it on post-operative day 1. Thirteen patients (46%) received CT of head within 1 – 30 days post-operatively (mostly for complains of headache). CT of head did not show any significant abnormality. All patients, but 4 were noticed to have no residual tumor on MRI after 3 months post-operatively. For 6 patients that received MRI on post-operative day 1, we found difficult to determine the amount of residual tumor when compared to MRI at 3 months. One patient underwent exploration transsphenoidal surgery for questionable rhinorrhea. **CONCLUSIONS:** The majority of the patients in our cohort received their first imaging after 3 months post-operatively as recommended by the AANS/CNS guidelines. No unexpected events were noticed. The timing of the MRI did not change treatment plans. We conclude that following evidence-based guidelines for the first post-operative imaging is safe and certainly more cost effective.

NIMG-102. APPLICATION OF CALCITRIOL TO ENHANCE THE QUALITY OF IMAGING WITH 5-ALA FLUORESCENCE-GUIDED RESECTION OF GLIOMA

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BACKGROUND: Recurrence of glioma frequently occurs within the marginal area of the surgical cavity as a result of residual infiltrating glioma cells. It has been demonstrated that more extensive surgical resection appears to be associated with longer life expectancy for patients with high grade glioma. Fluorescence-guided surgery with 5-aminolevulinic acid (ALA) for resection of glioma has been used as an effective therapeutic modality to improve recognition of brain tumor margin and patient prognosis. However, the marginal area of glioma usually shows vague or no fluorescence, which makes tumor identification difficult. **METHODS:** To be able to understand how to overcome these issues, we assessed the intracellular levels of PpIX and quality of 5-aminolevulinic acid metabolic imaging in human glioma cell lines and rat cortical astrocytes preconditioned with calcitriol for 48 hours by flow cytometry and fluorescence microscopy. Furthermore, expression of porphyrin synthetic enzymes in pretreated glioma cells was analyzed by RT-PCR and changes in ALA-induced PpIX fluorescence and cell survival after light exposure were assessed. **RESULTS:** Calcitriol pretreated glioma cells showed higher level of ALA-induced PpIX than control group. Interestingly, this study revealed that pretreatment of normal astrocytes with calcitriol followed by ALA did not result in increased intracellular concentrations of ALA-induced PpIX. Furthermore, mechanistic studies demonstrated that calcitriol enhanced the accumulation of ALA-induced PpIX via upregulation of CPOX. **CONCLUSION:** This finding suggests that the combined treatment of glioma cells with calcitriol, a simple, non-toxic and highly effective preconditioning regimen, may provide an effective and selective therapeutic modality to enhance ALA-induced PpIX fluorescent quality and improve recognition of tumor tissue.

NEUROTOXICITY OF CANCER TREATMENT

NTOX-03. NEUROLOGIC COMPLICATIONS OF CTLA-4 INHIBITOR IPILIMUMAB

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BACKGROUND: Neurologic complications are an increasingly recognized complication of the use of the immune checkpoint inhibitors in the treatment of solid tumors. The clinical spectrum of the CTLA-4 immune checkpoint inhibitor ipilimumab associated neurologic complications and optimum treatment approach is not established. **OBJECTIVES:** To determine the frequency, clinical spectrum and optimum treatment approach to CTLA-4 inhibitor associated neurologic complications. **METHODS:** This single center, retrospective cohort study was conducted from the drug's FDA approval, March 2011 to December, 2016. All patients receiving a CTLA-4 inhibitor were identified using the Mayo Cancer Pharmacy database. Patients who developed neurological symptoms in immediate temporal proximity to Ipilimumab use were included. We excluded patients who developed symptoms after subsequent immune-modulatory or cancer related treatments (e.g. PD-1 inhibitors), or patients with symptoms referable to metastatic disease. **RESULTS:** 445 patients received ipilimumab at our institution between March 2011 and January 2016. 222 (49.8%) had been evaluated by a staff neurologist at our institution during their care. 3 patients (0.6%) were felt to have neurologic phenomenon in proximity to dosing of ipilimumab which was potentially attributable to the medication while not on another immune checkpoint inhibitors. Two patients (66%) had transient self-limited cranial neuropathies (Bell's palsy; transient diplopia). One patient (33%) had bilateral phrenic nerve inflammatory neuropathies with diaphragmatic failure and simultaneous pan-hypopituitarism while being treated with ipilimumab. In our cohort multiple patients (n= 13, 2.9%) who had previously received ipilimumab subsequently were treated with PD-1 inhibitors and developed neurologic complications. **CONCLUSIONS:** Neurological adverse events associated with the CTLA-4 inhibitor ipilimumab in our large cohort consisted of transient self-limited cranial neuropathies and one case of inflammatory amyotrophy which responded to discontinuation of ipilimumab and initiation of steroids, with an incidence of 0.6%. Discontinuation and immune rescue may be indicated.

NTOX-04. INVESTIGATION OF N-ACETYLCYSTEINE FOR THE PREVENTION OF CISPLATIN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENTS

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OBJECTIVES: Chemotherapy-related cognitive impairment (CRCI) is a major clinical problem, which diminishes the quality of life of cancer sur-

vivors. We focus on the neurocognitive impairments provoked by cisplatin, a chemotherapy agent widely used as treatment for various malignancies including ovarian, testicular, head and neck cancers, and pediatric brain tumors. More than 30% of advanced ovarian cancer patients develop CRCI during and after cisplatin-based chemotherapy. We examined mitochondrial dysfunction as a mechanism underlying cisplatin CRCI, and the ability of the antioxidant N-acetylcysteine to mitigate these toxicities in a rat model, and *in-vitro* in cultured rat hippocampal neurons and neural stem/progenitor cells (NSC). **METHODS:** We examined the effects of cisplatin on neuronal morphology, apoptosis, and cognition in rats. We assessed the effects of cisplatin on mitochondrial respiratory function, reactive-oxygen species (ROS) production, caspase-9 activation, and glutathione levels *in-vitro*. **RESULTS:** Cisplatin reduced neuronal dendritic branching and spine density and induced apoptotic cell death in the rat hippocampus. Chronic cisplatin treatment impaired cognitive function; this impairment was mitigated by N-acetylcysteine administration. *In-vitro,* cisplatin damaged mitochondrial DNA, impaired respiratory activity, elevated ROS levels, and depleted glutathione. N-acetylcysteine mitigated cisplatin-induced neural ROS levels and glutathione depletion, apoptotic cell death, and neuronal post-synaptic density-95 puncta loss, while not interfering with cisplatin's anti-cancer effect in two ovarian cancer cell lines when administered 10 h following cisplatin. **DISCUSSION:** The cognitive deficits caused by cisplatin in rats result from the loss of excitatory synapses and dendritic spines that anchor them, as well as from injury to mature and developing neurons. This neuronal toxicity derives from mitochondrial damage. Importantly, treatment with N-acetylcysteine mitigates cisplatin-induced neurotoxicity and cognitive deficits. We are planning a Phase I study to examine if NAC administration to ovarian cancer patients receiving cisplatin is safe, and if it ameliorates the cognitive deficits previously described in this patient population.

NTOX-06. INCREASE OF PSEUDOPROGRESSION AND TREATMENT RELATED EFFECTS IN LOW-GRADE GLIOMA PATIENTS TREATED WITH PROTON RADIATION AND TEMOZOLOMIDE

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INTRODUCTION: Chemoradiation with temozolomide (TMZ) can be associated with pseudoprogression (PsP) in glioblastoma. The occurrence of early or delayed treatment effects and pseudoprogression is less well understood in low-grade gliomas (LGG). We hypothesized that adding TMZ to radiotherapy might increase the incidence of treatment related effects or pseudoprogression. **METHODS:** Chart review and volumetric MRI-analysis was performed on 109 chemotherapy-naïve patients with grade I-II or IDH1-mutant grade III glioma treated with proton-radiotherapy (RT) between 2005-2015. Progression was defined by tissue-diagnosis or new chemotherapy-initiation. Post-treatment related effects (PTRE) were defined as increase in T2/FLAIR or new/increase in abnormal enhancement without evidence of tumor progression or growth 6-12 months later. PsP was defined if a lesion meeting PTRE-criteria was suspicious for progression or volumetrically increased at least 40% from baseline. Late-PsP was defined as PTRE occurring more than 12 months after RT. Pearson's chi-squared test was used for statistical analysis. **RESULTS:** Median RT-dose was 54 Gy (RBE) (range: 45-60). There were 70, 27, and 12 patients who respectively received RT alone, RT with concurrent-TMZ, and RT with adjuvant (sequential)-TMZ. PsP was not more common with concurrent-TMZ versus adjuvant-TMZ (PsP: 67% versus 83%; p=0.29; enhancing-PsP: 52% versus 58%; p=0.710). However, PsP was significantly more frequent with TMZ+RT versus RT alone (PsP: 72% versus 39%; p<0.001; enhancing-PsP: 54% versus 34%; p=0.047). There were no significant inter-group-differences in mean-change from pre-RT-baseline in KPS, MMSE, or seizures during the year following RT-initiation. PsP was significantly more common in presence of p53-mutation (PsP: 62% versus 38%; p=0.048; enhancing-PsP: 48% versus 29%; p=0.124), but unrelated to IDH1-mutant status (PsP: 59% versus 38%; p=0.101; enhancing-PsP: 43% versus 43%; p=1.0) and MGMT promoter methylation (PsP: 66% versus 47%; p=0.296; enhancing-PsP: 50% versus 47%; p=0.876). **CONCLUSIONS:** Treatment with TMZ and p53-mutation status were associated with increased PsP in LGGs treated with proton-radiotherapy.

NTOX-08. CYSTIC ENLARGEMENT DURING CHEMOTHERAPY AND GROWING TERATOMA SYNDROME IN NON-GERMINOMATOUS GERM CELL TUMOR

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BACKGROUND: The term "growing teratoma syndrome (GTS)" was used with an extended interpretation from original report by Logothetis et al. as patients with germ cell tumors who present with enlarging original/metastatic masses during or after appropriate systemic chemotherapy despite normalized serum markers. In other words, the definition of the term GTS is not fully established. In this study, we defined primary GTS (p-GTS) as the patients who developed cystic enlargement during treatment, and recurrent GTS (r-GTS) as the patients who developed enlargement of teratoma after CR of initial tumors as reported by Logothetis et al. We analyzed the risk of GTS in the patients with non-germinomatous GCT (NGGCT). **MATERIALS AND METHODS:** Between 2003 and 2017, we treated 14 patients (14 male; age ranging 5.4 to 51.9, median 13.8) with NGGCT at our institution of which two were surgically removed before chemotherapy and were excluded. We reviewed the changes in imaging features in 12 patients with NGGCT during this treatment period. **RESULTS:** Among 12 patients, 1 patient achieved CR. In 11 non-CR patients, we surgically confirmed mature/immature teratoma component. Six of 11 patients showed p-GTS, and three showed enlargement of total tumor volume despite decrease in the volume of solid components. Among 3, only one patient completed the planned protocol of chemotherapy and radiotherapy. One was asymptomatic but had to stop chemotherapy, and the other developed hearing disturbance followed by altered consciousness resulting from compression of brainstem and underwent surgical removal after discontinuing radiochemotherapy. One patient developed r-GTS. Patients with the cyst less than 5mm did not develop the p-GTS. However, no imaging feature was predictive for GTS in our results. **CONCLUSIONS:** The incidence of p-GTS is not rare. Physicians need to be aware of this important phenomenon. Future study is necessary to confirm the etiology and predictive factor of GTS.

NTOX-09. RECOMMENDED PHASE II DOSE OF INTRA-ARTERIAL MELPHALAN GIVEN WITH INTRA-ARTERIAL CARBOPLATIN, OSMOTIC BLOOD-BRAIN BARRIER DISRUPTION AND DELAYED OTOPROTECTIVE SODIUM THIOSULFATE FOR PATIENTS WITH RECURRENT OR PROGRESSIVE CNS EMBRYONAL OR GERM CELL TUMORS

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INTRODUCTION: Intra-arterial chemotherapy in conjunction with transient osmotic BBB disruption (IA/BBBD) has been shown to increase drug delivery (10-100 folds) to the CNS. We report the maximum tolerated dose of IA melphalan in combination with IA carboplatin with BBBD and delayed IV sodium thiosulfate (STS) otoprotection for patients with recurrent or progressive CNS embryonal or germ cell tumors. In Prior studies, STS has been shown to protect against carboplatin-induced hearing loss. **METHODS:** This prospective single-institution phase I/II trial was approved by the institutional review board (NCT00983398). Subjects with embryonal and germ cell tumors of the CNS between 1 and 45 years of age, and met the inclusion/exclusion criteria received IA carboplatin (200 mg/m2/day x two days) and melphalan (starting at 4 mg/m2 x two days with inter-patient 3X3 dose escalation as per protocol until the MTD was reached) in conjunction with osmotic BBBD on two consecutive days every 4-6 weeks for up to 12 treatment cycles. For otoprotection, IV STS was given four and eight hours after carboplatin. **RESULTS:** 10 males and 4 females (median age 16.3 years, 1.7-28.6 yrs) were enrolled. 11/14(79%) had objective radiographic responses (4 PR, 7 SD). Most frequent grade 3 or 4 toxicities were hematological (64%) with only 1/14 patients developing ototoxicity (Brock's grade-4). The maximum tolerated dose of IA Melphalan was 6 mg/ m2 x 2 days. **CONCLUSION:** The recommended dose phase II dose of melphalan is 6 mg/m2 IA x 2 days when given with IA carboplatin administered with BBBD and delayed IV STS for otoprotection. Favorable safety profile, objective responses and excellent hearing protection compared to IA/BBBD carboplatin without STS warrants proceeding with the phase II part of this study. Phase I study will continue for subjects younger than 10 years due to limited accrual in this age group.