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SIOP CNS GCT II aimed to establish if 24Gy Whole Ventriculocerebrotherapy (WVRT) in localised germinoma is sufficient for tumour control. After central review of radiological response following ‘CarboPEI’ chemotherapy, patients in complete remission (CR) were consolidated with 24Gy WVRT. Between 2/2007 and 2/2018, 182 patients from 8 European countries with histologically-confirmed fully-staged localised germinoma were registered. 70 patients were in CR after chemotherapy, 98 in partial remission (PR), seven had stable disease, two progressive disease, and in five no response data were documented. Of the 70 patients in CR, 58 received 24Gy WVRT alone; two of these relapsed, one local and one disseminated, two and six years after diagnosis. Of the 98 patients in PR after chemotherapy, 86 received 24Gy WVRT and 16Gy boost, of which five relapsed (three local, two distant). Up to 12 months from diagnosis, 69% of 70 patients in CR received WVRT only, 48% of 58 with WVRT only and 9% of 32 with placebo. Therapeutic gains were observed in improving radiological disease control, evidence of tumour shrinkage, and in some cases, tumour resolution. The median follow-up was 3.7 years. Event-free survival (EFS) for patients in CR and with WVRT only (n=58) was 98% at 4 years. 4-years EFS of patients with PR and WVRT 24Gy and WVRT boost (n=86) was 95%. Localised germinoma in CR after chemotherapy had an excellent outcome with 24Gy WVRT alone; 24GY WVRT can therefore be considered the standard consolidation treatment in this group. International consensus on radiological response criteria is of utmost importance to avoid overtreatment of such patients and to pave the way for further treatment reduction in this group of patients.

HIGH GRADE GILOMIA

HGG-01. ENTRETCINIB IN RECURRENCE OR REFRACTORY SOLID TUMORS INCLUDING PRIMARY CNS TUMORS: UPDATED DATA IN CHILDREN AND ADOLESCENTS

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STARTCK-NK (phase 1/2) is evaluating entrectinib, a CNS-penetrant oral, TRK/ROS1/ALK tyrosine kinase inhibitor, in patients <21 years with recurrent/refractory solid tumors, including primary CNS tumors. After dose-escalation recommended dose, 55 patients were treated in all-comers, cohorts with gene-fusion-positive CNS/solid tumors (NTRK/ROS1/ALK) are being enrolled. As of 5Nov2019 (data cut-off), 39 patients (4.9m-20y; median 7y) have been evaluated for response, classified as complete (CR) or partial response (PR), stable (SD) or progressive disease (PD) using RANO CNS, RECIST (solid tumors) or Curie score (neuroblastoma). Responses in patients with fusion-positive tumors were Investigator-assessed (BICR assessments are ongoing) and occurred at doses ≥400mg/m². Best responses in fusion-positive CNS tumors (n=14) were: 4 CR (GAP1-NTRK2, ETV6-NTRK3), 5 PR (EML4-NTRK2), 5 EML4-ROS1, 5 ETV6-NTRK3, TPR-NTRK1, EEF1G-ROS1; 3 SD (BCR-NTRK2, ARHGEF2-NTRK1, KIF21B-NTRK1); 2 PD (PARP6-NTRK3, EML4-ALK); and in fusion-positive solid tumors (n=8) were: 3 CR (ETV6-NTRK3, DCTN1-ALK), 5 PR (EML4-ALK), TSG-ROS1; three (KIF1B-ALK). Best responses (Investigator-assessed) in non-fusion tumors (n=17) were: 1 CR (ALK F1174L mutation), 3 SD, 10 PD, 3 no data/unevaluable. The objective response rate (CR+PR/total) in patients with fusion-positive tumors was 77% (1/22) versus 6% (1/17) in those with non-fusion tumors. All 39 patients experienced ≥1 adverse event (AE); the most frequent AEs included weight gain and anemia (both 48.7%); increased ALT, increased AST, cough and pyrexia (all 46.2%); increased creatinine and vomiting (both 43.6%); and bone fractures (n=10, in 9 patients). Entrectinib has produced striking, rapid, and durable responses in solid tumors with target gene fusions, especially high-grade CNS neoplasms.

HGG-02. ADOLESCENT AND YOUNG ADULT (AYA) GILOMIA WITH BRAF V600E MUTATION

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BACKGROUND: Biological features of pediatric glioma differ significantly from those of adult glioma, and limited data are available on those of AYA patients. Here, we focused on AYA patients with glioma, especially those harboring BRAF V600E mutation, and investigated their clinical and biological features. METHODS: We retrospectively analyzed AYA patients with brain tumors harboring BRAF V600E who were treated in two hospitals in Japan. RESULTS: Clinical information was available for 14 patients. The median age at diagnosis was 25 years (range: 15–38). Five patients were diagnosed with glioblastoma (GBM), including one epithelioid type. These patients were over 25. Although one patient with GBM died of the disease 6.9 years after initial diagnosis, the remaining patients were alive. Two patients were alive without recurrence at 58 and 51 months after the treatment. The patient with epithelioid glioblastoma experienced early recurrence (the remaining nine patients (64%) were diagnosed with low-grade glioma, including ganglioglioma, pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, pleomorphic xanthoastrocytoma, and polymorphous low-grade neuroepithelial tumor of the young. No patients died of the disease and four patients are still alive without recurrence after initial treatment without adjuvant treatment. Two patients are (epithelioid glioblastoma and ganglioglioma) currently undergoing treatment with a BRAF inhibitor for recurrent tumors. DISCUSSION: Although the number of this study is limited, our study suggested that the prognosis of AYA patients with BRAF V600E positive GBM may not be as dismal as that of children or adults.

HGG-04. ZINC ENHANCES TEMOZOLOMIDE CYTOTOXICITY IN PEDIATRIC GLIOBLASTOMA MULTIFORME MODEL SYSTEM

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BACKGROUND: Temozolomide (TMZ) is an alkylating agent that has become the mainstream treatment of the most malignant brain cancer, glioblastoma multiforme (GBM). Unfortunately only a limited number of patients respond to it positively. We have shown that the TMZ sensitivity in adult GBM is vitro and also in vivo this effect has not been tested with pediatric GBM. METHODS: Using Human pediatric glioblastoma cell lines- KNS42 (mutant p53/ MGMT [-]) and SF188 (mutant p53/ MGMT [+] ), we investigated whether addition of zinc to TMZ enhances its cytotoxicity against GBM. RESULTS: In vitro cell viability analysis showed that the cytotoxic activity of TMZ was substantially increased with addition of zinc and this response was accompanied by an elevation of p21, PUMA, BAX, BAK, and decrease in growth factor expression by low k67. Beta-gal analysis showed that most of the remaining cells after the combination therapy are in senescence state. In order to eliminate the senescent population created as a result of the combined treatment of TMZ and Zn, we decided to use a senolytic agent Navitoclax (ABT-263) that was demonstrated to be effective in rescuing senescent cells by specific in vitro
Abstracts

HGG-05. REGRESSION OF RECURRENT GliOBlastoma AFTER BORON NeUTRON CAPTURE Therapy AND CHIMERIC ANtigen RECEPTOR T-CELL THERAPY IN A CHILD
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A 6 y/o girl with recurrent multifocal glioblastoma received 3 times of boron neutron capture therapy (BNCT) and chimeric antigen receptor CAR-engineered T cells targeting the tumor-associated antigen HER2. Multiple infusions of CAR T cells were administered over 30 days through intraventricular delivery routes. It was not associated with any toxic effects of grade 3 or higher. After BNCT and CAR T-cell treatment, regression of all existing intracranial lesions were observed, along with corresponding increases in levels of cytokines and immune cells in the cerebrospinal fluid, but new lesions recurred soon after the treatment. This clinical response continued for 14 months after the initiation of first recurrence.

HGG-06. REMARKABLE RESPONSE TO BRAF INHIBITOR IN AN INFANT WITH DESEMINATED INFANTILE LEPTOMENINGEAL GLIONEURONAL TUMOR (DLGNT)
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INTRODUCTION: Diffuse Leptomeningeal Glioneuronal Tumors (DLGNT) are rare CNS tumors and in infants, they can be lethal. There are several anecdotal reports in infants with low grade gliomas (LGG) with treated with BRAF inhibitors. METHODS: A six-month old baby girl presented with a history of absent weight gain and vomiting. Imaging revealed a 4.7 x 4.2 x 2.8 cm suprasellar and multiple small extra-axial plaques in the temporal lobe. The child developed significant ascites post VP shunt requiring shunt extenlization, externalized protein infusin support and hospitalization for six weeks. Immunohistochemistry revealed focal Olig-2 and Syn1 positivity. EMA showed patchy cytoplasmic reactivity in stromal cells and multiple small extra-axial plaques in the occipital lobe. IN1-1, IDH-1, and CD117 were negative, Ki67 proliferation index was 8-10%. ICR for BRAF V600E mutation was detected. BRAF was negative. This was confirmed by Genome Wide Next Generation Sequencing. While waiting for GNS testing results, the baby received one dose of Vindastine. However, within seven days of initiating Debrafenib, significant clinical and radiological responses were observed. CONCLUSION: The baby continued to be ameliorated without any side effects. Unfortunately, follow-up MRI showed local tumor recurrence at 3-months post-surgery. The family agreed to the initiation of oral larotrectinib as a less invasive therapy. The patient tolerated Larotrectinib very well with no reported adverse effects. Follow-up MRI performed 5 months post-larotrectinib treatment and showed significant tumor regression, indicating an excellent treatment response. CONCLUSION: This case highlights how TRK-inhibitors can be integrated as a first-line therapy for pediatric high grade GBMs harboring TRK-fusions. We also highlight the need for the integration of genomic profiling and molecular analysis into the routine histopathological analysis of pediatric patients with malignant primary intracranial tumors, to detect any genetic mutations that can be targeted with available therapies to avoid the morbidity associated with non-precision conventional therapies.

HGG-07. CYCLIN-DEPENDENT KINASES AS TARGET STRUCTURES FOR CANCER THERAPY – A COMPARATIVE IN VITRO ANALYSIS ON PATIENT-DERIVED GliOBlastOMA CELl CELLULAR MODELS
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INTRODUCTION: Current therapeutic approaches have limited clinical success for Glioblastoma patients, making novel strategies urgent. Cyclin-dependent kinases (CDKs) are crucial in cell cycle, oncogenic transcription, DNA repair, and stem-cell renewal. Glioma cells frequently show genomic alterations in CDKs. Here, we evaluated the antimortal activity of selective CDK inhibitors (CDKI) abemaciclib (CDKI4/6), palbociclib (CDKI4/6), and dinaciclib (CDKI12/5/9) alone and in combination with chemo-radiotherapy. MATERIALS/METHODS: Low passage glioblastoma cell lines (N=5) with different molecular characteristics were cultured in 2D and 3D (neurophosphores (NSP), glioma stem-cells (GSC)). The impact of CDKI alone or in combination with TMZ and radiation (2Gy) was examined. Viability was measured using Calcein-AM and 3D-Glo assays; DNA double-strand breaks by γ-H2AX immunofluorescence. Functional analyses were performed from a 2D culture (72h treatment). RESULTS: Dinaciclib significantly affected viability of GBM cell lines even shortly after low-dose treatment. CDKI 4/6 inhibitors were less effective. Abemaciclib and dinaciclib acted radio-sensitizing. Dinaciclib combined with different substances (72h, dose: IC50) synergistically potentiated antitumoral effects. In a scratch assay, abemaciclib decreased wound healing; dinaciclib even induced cell death. Microarray analysis revealed altered gene expression: Genes mediating cell adhesion, division, DNA-binding, apoptosis (Casp3, Casp8), senescence (AS1F1, CENPA, FBXO31), and autophagy (ATG4D, ATG2A, SOGA1) were upregulated. Chemotaxis-mediating (CXCL8, CCLI20) and proteases like JUNB and FABP1 were downregulated. Long-term treatment induced dinaciclib resistance in 1/5 cases, and none abemaciclib-treated cells. This was reversed when dinaciclib was combined with TMZ. CONCLUSION: Our results demonstrate strong anti-GBM activity of dinaciclib and abemaciclib, with additive effects of chemotheraphy and radiosensitization, encouraging to move forward this strategy.

HGG-08. First LINE THERAPY OF PEDIATRIC GliOBlastOMA WITH LAROTRECIbIN
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PURPOSE: In this case report, we document new recommendations for the treatment of pediatric glioblastoma based on a genetic understanding of the disease. METHODS AND RESULTS: A Saudi girl aged 18 months presented with a history of right sided weakness and partial seizures. MRI revealed the presence of large complex left frontal tumor. Craniotomy and gross total resection were performed. Post-operatively The patient showed excellent recovery with no neurological deficits. Pathological diagnosis confirmed GBM III. Due to the expected poor survival, the patient’s family declined standard therapy, including chemotherapy and/or radiation therapy. RESULTS: Molecular analysis showed positive fusion mutations for ETFV-ENTRK3 making the patient an ideal candidate for larotrectinib (an irreversible and selective TRK inhibitor). Unfortunately, follow-up MRI showed local tumor recurrence at 3-months post-surgery. The family agreed to the initiation of oral larotrectinib as a less invasive therapy. The patient tolerated Larotrectinib very well with no reported adverse effects. Follow-up MRI performed 5 months post-larotrectinib treatment and showed significant tumor regression, indicating an excellent treatment response. CONCLUSION: This case highlights how TRK-inhibitors can be integrated as a frontline therapy for pediatric high grade GBMs harboring TRK-fusions. We also highlight the need for the integration of genomic profiling and molecular analysis into the routine histopathological analysis of pediatric patients with malignant primary intracranial tumors, to detect any genetic mutations that can be targeted with available therapies to avoid the morbidity associated with non-precision conventional therapies.

HGG-11. HIGH-GRADE GliOMAs IN ADOLESCENTS AND YOUNG ADULTS HIGHLIGHT HISTOMOLECULAR DIFFERENCES WITH THEIR ADULT AND PEDIATRIC COUNTERPARTS
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