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Raloxifene sensitizes glioblastoma cells to hypoxia-induced death through inhibition of stress granule dissolution

A Robichaud (Halifax) K Attwood (Halifax) A Balgi (Vancouver) M Roberge (Vancouver) A Weeks (Halifax)*

Background: Glioblastoma (GBM) is the most common primary malignant brain tumour. Despite aggressive therapy, median survival is only 14 months. Death typically results from treatment failure and local recurrence. The GBM microenvironment is highly hypoxic, which correlates with treatment resistance. Cytoplasmic RNA stress granules (SGs) form in response to hypoxic stress and act as sights of mRNA triage, allowing preferential translation of pro-survival mRNA during stress. We hypothesize that SGs may play a role in hypoxia-induced resistance to therapy, and may be targetable by chemotherapeutics to improve outcomes. **Methods:** We screened 1280 approved compounds to identify drugs that inhibited formation or dissolution of SGs in U251 glioma cells. Raloxifene inhibited SG dissolution in a dose dependent manner. We treated cells with raloxifene and incubated them in hypoxia, and then measured rates of cell death using cell counting and Presto blue. **Results:** Cell death rates were synergistically higher in cells treated with the combination of raloxifene and hypoxia compared to either treatment alone. **Conclusions:** Raloxifene inhibits the dissolution of SGs in glioma cells, and combination treatment results in synergistic tumour cell death. Taken together, this provides evidence that inhibition of SG dissolution may be a viable target for future GBM chemotherapeutics.

P.043

Volumetric analysis of low-grade glioma growth in serially-imaged patients

C Gui (London) JC Lau (London) SE Kosteniuk (London) JF Megyesi (London)*

Background: Diffuse low-grade gliomas (LGGs) are infiltrative, slow-growing primary brain tumors that remain relatively asymptomatic for long periods of time before progressing to aggressive high-grade gliomas. **Methods:** We retrospectively identified LGG patients that were stably managed by observation with numerous (≥ 8) serial magnetic resonance imaging (MRI) studies. Tumour volumes were measured by manual segmentation on imaging to study the growth of the lesion. Patient demographic information, tumour characteristics, and histological data were collected from electronic medical records. **Results:** Of 74 LGG patients, 10 (13.5%) patients were included in the study. The number of MRIs acquired ranged from 8 to 18 (median, 11) over a median of 79.7 months (range, 39.8-113.8 months). Tumor diameter increased at a median rate of 2.17 mm/year in a linear trajectory. Cox regression analysis revealed that initial tumour volume predicted time to clinical intervention, and Mann-Whitney U test found that patients diagnosed prior to age 50 had significantly slower-growing tumors. Clinical intervention was more likely for tumours larger than 73.8 mL. **Conclusions:** We retrospectively analyzed the natural history of LGGs in patients with numerous serial MRIs managed at a single institution.

Comparisons to the literature suggest that this is a subset of particularly slow-growing and low-risk tumours.

P.044

Salvage therapy in recurrent pediatric medulloblastoma: A single centre experience

MM Kameda-Smith (Hamilton) A Wang (Hamilton) A Adile (Hamilton) B Manoranjan (Hamilton) R Voth (Hamilton) A Sergeant (Hamilton) A Maharaj (Hamilton) O Ajani (Hamilton) B Yarascavitch (Hamilton) C Alyman (Hamilton) C Samaan (Hamilton) F Farrokhyar (Hamilton) J Duckworth (Hamilton) SK Singh (Hamilton) A Fleming (Hamilton)*

Background: Children diagnosed with medulloblastoma (MB) that are refractory to upfront therapy or experience recurrence have very poor prognoses. Reports of phase I and II studies for these children exist, but bear significant treatment related morbidity and mortality. **Methods:** A retrospective review of children diagnosed with a pediatric MB from 2002-2015 from the McMaster Pediatric Brain Tumour Study Group (PBTSG) captured a number of pediatric recurrent MB. **Results:** Over the 13-year period, 31 children with a histological diagnosis of MB were treated. At two years, 21 (67.7%) of 31 patients were free of recurrence and 25 (80.6%) survived. Thirteen children had recurrent or treatment refractory MB. mean time to recurrence was 14.6 months. The mean follow-up for survivors of recurrent MB was 4.0 years. In 3 recurrent MB, the disease had significantly progressed and the patients palliated. For the remaining children, therapy offered included surgery, radiation, and chemotherapy agents either in isolation or in varying combinations. **Conclusions:** Recurrent MB in our cohort carried a poor prognosis despite administration of salvage therapy. Though there is standardization of the upfront treatment exists, we observed great heterogeneity in the treatment of our 13 patients experiencing recurrence. A greater understanding of the biology of recurrent MB has the potential to guide salvage therapy.

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Flow cytometry in cerebrospinal fluid: utility in the diagnosis of central nervous system lymphoma

K Au (Calgary) S Latonas (Calgary) A Shameli (Calgary) I Auer (Calgary) C Hahn (Calgary)*

Background: Flow cytometry in the cerebrospinal fluid (CSF) is used as an adjunct to cytology to increase the sensitivity of detecting central nervous system (CNS) lymphoma. We aim to evaluate CSF flow cytometry as a diagnostic tool for lymphoma in patients presenting with undifferentiated neurologic symptoms. **Methods:** We retrospectively reviewed all CSF flow cytometry samples sent in the Calgary region from 2012-2015. Clinical data, laboratory investigations, radiologic imaging studies, and pathological data were analyzed. Clinical review extended to 2 years post CSF flow cytometric testing. **Results:** The number of samples of CSF flow cytometry that were positive for a hematological malignancy was 43/763 (5.6%). The overall sensitivity of the test was 72.9%. A positive result was more likely to occur in patients with a prior history of a hematological