Despite decades of trials, the prognosis for diffuse intrinsic pontine gliomas (DIPG) remains dismal. DIPG is inoperable and standard treatment is radiation alone, as the addition of chemotherapeutic agents, such as temozolomide, have not improved survival. In addition to inherent chemoresistance, treatment of DIPG is impeded by an intact blood-brain barrier (BBB). VAL-083 is a structurally unique bi-functional DNA-targeting agent that readily crosses the BBB. VAL-083 forms interstrand DNA crosslinks at N7-guanine, resulting in DNA double-strand breaks (DSB), S/G2-phase cell-cycle arrest, and ultimately cancer cell death. We have previously demonstrated that VAL-083 is able to overcome temozolomide-resistance in vitro and in vivo, and that its cytotoxicity is independent of the DNA-repair enzyme O6-methylguanine DNA-methyltransferase (MGMT). MGMT is almost universally expressed in DIPG and its expression is strongly correlated with temozolomide-resistance. VAL-083‟s distinct mechanism-of-action suggests the potential for combination with inhibitors of DNA DSB repair or S/G2 cell-cycle progression (e.g. Wee1 inhibitor AZD1775). Here, we investigated the effects of VAL-083 in combination with radiation, AZD1775 or irinotecan (topoisomerase inhibitor) in three DIPG cell-lines: SF10693 (H3.1), SF8628 (H3.3) and NEM157 (H3.3). VAL-083 showed activity at low uM-concentration in all three cell-lines. In addition, VAL-083 showed synergy with AZD1775 in all three cell-lines. Combined with its ability to cross the BBB, accumulate in brain tumor tissue and overcome MGMT-related chemoresistance, these results suggest VAL-083 as a potentially attractive treatment option for DIPG as single agent or in combination with AZD1775. Combination studies with radiation are ongoing and will be presented at the meeting.

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doi:10.1017/cjn.2018.287

Phase 2 studies of dianhydrogalactitol (VAL-083) in patients with glioblastoma, MGMT-unmethylated

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Current standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Most tumors recur within a year from diagnosis and median survival for recurrent GBM (rGBM) is 3-9 months. Unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance, exhibited by most GBM patients. VAL-083 is a DNA-targeting agent with a mechanism-of-action that is independent of MGMT. VAL-083 overcomes temozolomide-resistance in GBM cell-lines, cancer stem cells, and in vivo models. VAL-083 readily crosses the blood-brain barrier and accumulates in brain-tumor tissue. We recently completed a VAL-083 dose-escalation trial in temozolomide- and bevacizumab-refractory rGBM and determined that 40mg/m2/day given intravenously on days 1,2,3 of a 21-day cycle is generally well-tolerated. This dosing regimen was selected for subsequent GBM trials, including an ongoing single-arm, biomarker-driven Phase 2 trial (N=48) in temolozomide-refractory, bevacizumab-naïve rGBM , MGMT-unmethylated (Clinicaltrials.gov:NCT02717962). The primary objective of this study is to determine if VAL-083 improves OS compared to a historical control of 7.15 months for MGMT-unmethylated rGBM patients treated with lomustine (EORTC26101). In addition, another single-arm, biomarker-driven, Phase 2 study (N=25) of VAL-083 in combination with radiotherapy in newly diagnosed GBM, MGMT-unmethylated is ongoing (Clinicaltrials.gov:NCT03050736). This trial aims to determine a dose for further study of VAL-083 in combination with radiotherapy and explore if VAL-083 improves PFS and OS compared to historical results in newly diagnosed GBM. Enrollment and safety data updates will be provided at the meeting. The results of these studies, if successful, may support VAL-083 as part of a new chemotherapeutic treatment paradigm for GBM.

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doi:10.1017/cjn.2018.288

Are gangliogliomas in children and adults disorders of nervous system development?

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INTRODUCTION: Gangliogliomas (GGs) are neuroepithelial tumours of the central nervous system (CNS) composed of mature ganglion cells or a mixed population of ganglion and glial cells. Microarray data of low grade gliomas (LGG) including GGs revealed overexpression of the Dlx2 gene, a homeobox gene essential for interneuron migration and differentiation. We hypothesized that GGs are arrested in development, and began to explore the role of the Dlx2 gene. BRAF rearrangements and BRAF V600E point mutations have been reported in pediatric LGG. METHODS: DLX2 expression was examined in GGs using immunofluorescence (IF) and immunohistochemistry (IHC) labelling of formalin fixed paraffin embedded (FFPE) tissue sections, along with staining of glial and neuronal markers. BRAF mutations were detected using a commercial antibody and/or sequence verification of the DNA extracted from the FFPE blocks. RESULTS: In the Discovery cohort 10/30 were DLX2+ (33.3%) and in the Validation cohort 15/40 were DLX2+ (37.5%). Of these 15 cases, 15 were GFAP+ (100%), 15 were synaptophysin and/or NeuN+ (100%), and 13 were OLIG2+ (86.7%); 6 had a BRAF V600E mutation (40.0%). For the Validation cohort of 40 GGs, 28 were OLIG2+ (70.0%); 13/28 co-expressed DLX2 (46.4%). 18/40 cases had a BRAF V600 mutation(17 V600E, 1 V600G; 45.0%) and 6/18 were DLX2+ (33.3%). CONCLUSIONS: DLX2 is expressed in GGs in both neuronal and glial marker expressing tumour cells. Our results support that GGs arise from CNS progenitors arrested at the neuronal-glial cell fate “decision” point.

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doi:10.1017/cjn.2018.289

Functional characterization of ribosomal RNA methyltransferase NSUN5 in glioblastoma

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Glioblastoma is the most common and malignant brain tumor with a median overall survival of 20.5 months. There is an urgent need to develop novel therapeutic strategies. Using a glioblastoma TCGA dataset, we have determined that high NSUN5 mRNA expression is strongly associated with poor survival in glioblastoma patients. NSUN5 is a ribosomal RNA (rRNA)

cytosine methyltransferase. Human NSUN5 is located in chromosome 7 and is completely deleted in the Williams-Beurren syndrome, a complex neurodevelopmental disorder. However, RNA targets of NSUN5 in mammals and its role in cancer are unknown. The objective of this project is to determine whether elevated NSUN5 changes rRNA methylation pattern and thereby leads to pro-tumorigenic translational reprogramming and pro-tumorigenic phenotypes in glioblastoma. Western blotting showed that NSUN5 is expressed in 7 out of 9 established glioblastoma cell lines and in 8 out of 12 primary patient-derived glioblastoma cell lines. Bisulfite sequencing confirmed that NSUN5 methylates C3782 of human 28S rRNA in glioblastoma cells. Functionally, overexpression of NSUN5 increases, whereas NSUN5 knockout decreases global protein synthesis and sphere formation in glioblastoma cells. More importantly, mice bearing intracranial NSUN5-expressing U87 tumors survived for a shorter time than mice bearing tumors derived from U87 control cells. Our results suggest that NSUN5 methylates 28S rRNA and may enhance cancer stem cell phenotypes and tumor formation and/or progression in glioblastoma. Experiments are ongoing to determine whether NSUN5 promotes tumor formation and/or progression through translational reprogramming in glioblastoma. This study may help identify novel therapeutic targets for glioblastoma.

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doi:10.1017/cjn.2018.310

Improvement of hearing with bevacizumab in a patient with neurofibromatosis type 2 and bilateral acoustic schwannomas

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BACKGROUND: Neurofibromatosis type 2 (NF2) is a rare genetic condition caused by mutations in the Merlin gene on chromosome 22. It results in acoustic neuromas (schwannomas) and other CNS tumors including meningiomas and ependymomas. Most patients develop hearing loss as a result of neuroma-driven destruction of auditory nerves. Surgery and radiation therapy remain the two most commonly recommended treatment options. However, there is a risk of further hearing loss with these procedures. There is emerging evidence that bevacizumab, a monoclonal antibody against VEGF-A, can shrink acoustic neuromas and mitigate hearing loss. CASE PRESENTATION: A 34-year-old female with bilateral acoustic neuromas from NF2 suffers partial hearing loss in the left ear and total hearing loss in the right ear after removal of the right-sided neuroma. Baseline MRI showed a left-sided acoustic neuroma (15 x 13 mm) and recurrence of the right-sided neuroma (18 x 14 mm). Bevacizumab was initiated at 5 mg/kg IV every 14 days. After 8 cycles, the patient reported marked improvement in hearing. At lower frequencies (< 1,000 Hz, the range of human voice), auditory thresholds improved by up to 60% of baseline, while at higher frequencies, improvements of up to 46% were seen. Repeat imaging showed no disease progression. CONCLUSIONS: Bevacizumab led to hearing improvement and prevention of disease progression after 8 cycles of therapy. This treatment should be considered in patients with NF2 and acoustic neuromas who wish to pursue a less-invasive treatment option with the potential of delaying progression and mitigating hearing loss.

ORAL PRESENTATIONS
11 MAY 2018

1115 - 1200
SESSION SIX ~ GLIOBLASTOMA

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doi:10.1017/cjn.2018.290

Durable complete responses observed in patients with recurrent high grade glioma treated with Toca 511 & Toca FC

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Toca 511 (vocimagene amiretrorepvec) is an investigational retroviral replicating vector that selectively infects dividing cancer cells, integrates into the genome and replicates due to immune defects in tumors. Toca 511 spreads through tumors and stably delivers the gene encoding an optimized yeast cytosine deaminase that converts the prodrug Toca FC (investigational, extended-release of 5-fluorocytosine) into 5-fluorouracil. In preclinical models, 5-fluorouracil kills infected dividing cancer cells, myeloid derived suppressor cells and tumor associated macrophages, enabling immune activation against the tumor. In this dose ascending Ph1 trial (NCT01470794), Toca 511 was injected into the resection cavity wall of patients with rHGG, followed by courses of oral Toca FC. Additional cohorts included combination with bevacizumab or lomustine. Across the Ph1 program, the safety profile remains favorable. Objective responses (ORs) were assessed by IRR using MRI scans prior to Toca FC treatment as baseline. ORs occurred 6-19 months after Toca 511 administration, suggesting an immunologic mechanism. The ORs were observed in 4 patients with IDH1-wildtype and 2 patients with IDH1-mutant tumors, including 5 complete responses (CRs) with the investigational therapy alone, and 1 CR in combination with bevacizumab. The median duration of response (mDoR) was 35.1+ months. As of AUG2017, all responders were CR and remain alive. In a 23-patient subgroup who received high doses of Toca 511 and met Ph3 trial criteria, mOS was 14.4 months, 3-year survival rate was 26.1%, and mDoR was 35.7+ months with a durable response rate of 21.7%. Data suggest a positive association of durable response with OS.

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doi:10.1017/cjn.2018.291

Timing of adjuvant treatments on glioblastoma survival: A retrospective cohort analysis based on the national cancer database

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Few studies investigated the associations between intervention modalities, timing, and survival in glioblastoma (GBM) patients. A total of 20511 eligible GBM patients underwent biopsy and