NEURO-ONCOLOGY

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EARLY EFFECTS OF SURGERY AND RADIOTHERAPY ON ACTIVITY LEVELS IN PATIENTS WITH BRAIN TUMOURS: PRELIMINARY DATA FROM THE BRAINWEAR TRIAL

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BACKGROUND: BrainWear is a phase II observational clinical trial which collects data on patient activity levels, fatigue, Quality of Life (QoL) and imaging in patients with brain tumours METHODS: Newly diagnosed patients were offered wrist worn accelerometers (Axivity AX3) to be worn continuously throughout their treatment (surgery, chemoradiotherapy or radiotherapy) to monitor physical activity. We collected standardised measures of QoL, fatigue, MRI imaging data and disease progression. Here, we report early results on activity data 5 days before and after treatment. RESULTS: Of 23 patients recruited, we report complete pre and post treatment data in 4 patients (2 HGG, 2 metastatic) who underwent craniotomy (2), fractionated radiotherapy (1) and SRS (1). Both craniotomy patients experienced an immediate 60 – 70% reduction in activity, and were successfully discharged at day 2 post-op even though their activity was still significantly reduced. Both patients recovered another 10% in their activity levels following discharge. Radiotherapy patients experienced no early change within 5 days of starting treatment. CONCLUSION: As expected craniotomy results in much larger changes in activity levels than SRS and radical radiotherapy. Activity levels recover post craniotomy, but this takes > 5 days.

Using wearable activity monitors in brain tumour patients is feasible, although there are multiple practical problems. Interpreting such data will require consideration of inpatient vs. outpatient settings.

INHIBITORS OF POLY(ADP-RIBOSE) GLYCOHYDROLASE (PARG) EXHIBIT SINGLE AGENT THERAPEUTIC ACTIVITY AND SENSITIZE GLIOBLASTOMA CELLS TO IONIZING RADIATION

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OBJECTIVE: The lack of an effective therapy for glioblastoma (GBM) largely results from the intrinsic resistance of GBM cells. The radiosensitizing activity of inhibitors of poly(ADP-ribose) polymerases (PARPs) highlights the important role of poly(ADP-ribose) (PAR) in the DNA damage response. In contrast to PARPs, inhibition of poly(ADP-ribose) glycohydrolase (PARG), the enzyme responsible for degrading PAR chains, has shown single agent therapeutic activity in non-glioma cancer cells. This work aims to validate the therapeutic potential of PARG inhibitors (PARGi) in GBM. RESULTS: Baseline PAR levels were found to vary between different primary and commercial GBM cells, with PARylation increasing upon exposure of cells to ionizing radiation (IR), as expected. Target engagement of a novel PARGi, PDD00017273, was confirmed by the accumulation of nuclear PAR in treated cells. Inhibitor specificity was demonstrated using an inactive control compound and by combining PARGi with the PARP inhibitor olaparib, which blocked the effect. Single agent treatment with PARGi reduced the clonogenic survival of GBM cells in a concentration-dependent manner. Importantly, PARGi also sensitized GBM cells to IR (sensitizer enhancement ratios, SER, ≥ 1.40)

CONCLUSION: In contrast to PARP inhibitors, novel PARGi exhibit single agent activity against a panel of GBM cell lines, and also show robust radiosensitizing activity. PARGi therefore have therapeutic potential in this cancer of unmet need.

Cell line	Type	Single agent activity (EC_{50} nM)	Radiosensitizing activity (SER)
E2 bulk	Primary	162	1.65
E2 stem-enriched	Primary	52	1.46
G7 bulk	Primary	91	1.49
G7 stem-enriched	Primary	283	1.42
T98G	Commercial	127	1.40

ROLE OF DIFFUSIONAL KURTOSIS IMAGING IN GRADING OF BRAIN GLIOMAS: A DIAGNOSTIC TEST ACCURACY SYSTEMATIC REVIEW AND META-ANALYSIS

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AIM AND OBJECTIVES: We aim to illustrate the diagnostic performance of diffusional kurtosis imaging (DKI) in the diagnosis of gliomas. METHODS AND MATERIALS: A review protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P), registered in the international prospective register of systematic reviews, PROSPERO and published. Literature search in 4 databases was performed using the keywords "glioma" and "diffusional kurtosis".After applying a robust inclusion/exclusion criteria, included articles were independently evaluated according to the QUADAS-2 tool.Data extraction was done in a pre-designed pro forma. Reported sensitivities and specificities were used to construct 2x2 tables and paired forest plots using the Review Manager (RevMan®) software. Random-effect model was pursued using the hierarchical summary receiver operator characteristics. RESULTS: Initially, 216 hits were retrieved. Considering duplicates and inclusion criteria; 23 articles were eligible for full-text reading. Ultimately, 19 studies were deemed to be eligible for final inclusion. Quality assessment revealed 9 studies with low risk of bias in the 4 domains. Using a bivariate random-effect model for data synthesis; summary ROC curve showed pooled area under the curve (AUC) of 0.92 and estimated sensitivity of 0.87 (95% CI: 0.78 - 0.92) in high/low grade gliomas' differentiation.A mean difference in Mean Kurtosis (MK) value between HGG and LGG of 0.22 [95% CI: 0.25 - 0.19] was illustrated (p value = 0.0014) and a moderate degree of heterogeneity (I^2= 73.8%). CONCLUSION: DKI shows good diagnostic accuracy in high/low grade gliomas' differentiation; which might qualify it to be part of the routine clinical practice, however; further evidence is deemed for technique standardization.

THE COLLAGEN-PROLYL HYDROXYLASES PROMOTE PROLIFERATION AND INVASION IN GBM

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Glioblastoma Multiforme (GBM) is the most aggressive form of brain tumour, with a median survival time of just 14 months. Current standard therapy includes surgical excision, followed by chemotherapy and radiotherapy, however complete surgical excision is not usually possible due to the diffuse and infiltrative nature of the disease. To combat this, therapies inhibiting the invasion of leader migratory cells are an attractive area of research. The collagen prolyl-4 hydroxylases (C-P4Hs) are a family of proteins which catalyse the hydroxylation of proline residues on pre-pro-collagen, leading to the formation of the stable triple-helical structure of functional collagen. Collagen is a highly abundant protein, and important in several oncogenic cellular processes including proliferation, invasion and migration. We hypothesis that by inhibiting the C-P4Hs, the pro-tumorigenic effect of collagen will be inhibited in GBM. To explore this, we treated cells with ethyl 3,4-dihydroxybenzoate (EDHB) (a C-P4H inhibitor) and observed the resultant effect in GBM cells lines and primary cells through proliferation assays and 3D tumour spheroid invasion assays. Our results indicate that the addition of EDHB significantly reduces proliferation and invasion in both cell lines and primary GBM samples. Furthermore, we show that the C-P4Hs are upregulated in hypoxic conditions, which are commonly found in the clinical tumour microenvironment. Our study reveals that the C-P4H proteins may be an attractive therapeutic target to reduce invasion and proliferation and may be especially attractive as adjuvants with a cytotoxic agent such as temozolomide.