NHMRC Clinical Trials Centre

COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

The achievement of better health outcomes for patients and those affected by brain tumours through clinical trials research

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10th COGNO ANNUAL SCIENTIFIC MEETING

Tailoring Therapies for Brain Tumours: Challenges and Opportunities

Monday 23rd - Tuesday 24th October 2017

Rydges Melbourne Hotel, VIC Australia

CONFERENCE BOOKLET

COGNO

COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

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2017 ASM ORGANISING COMMITTEE

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Dr Lawrence Cher	Neuro-oncologist, Olivia Newton John Cancer & Wellness Centre
Dr Anthony Dowling	Medical Oncologist, St Vincent's Hospital
Ms Marcia Fleet	Care Coordinator, Melbourne Health
Ms Dianne Legge	Care Coordinator, Olivia Newton John Cancer & Wellness Centre
Dr Jonathon Parkinson	Neurosurgeon, Royal North Shore Hospital
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Ms Yi Feng	Administrative Assistant, COGNO

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The achievement of better health outcomes for patients and those affected by brain tumours through clinical trials research

Dear Colleague

On behalf of the Organising Committee, welcome to the 10th COGNO Annual Scientific Meeting! The theme of this year's meeting is *'Tailoring Therapies for Brain Tumours: Challenges and Opportunities'*.

We are delighted to welcome the 2017 COGNO Outreach Education Preceptorship recipient, Dr Achiraya Teyateeti from Thailand.

We are excited to host three renowned international guest speakers:

- Professor Patrick Wen, MD
- Professor Daniel Kelly, MD
- Professor Koichi Ichimura, MD PhD

Highlights of our program include:

- Tailoring Therapies for Brain Tumour – Challenges and Opportunities
- Novel Treatment Strategies for Brain Tumours
- Seeing the Target – Updates in Diagnostics and Imaging
- Hitting the Targets – Updates in Treatment
- Treating the Patient, Not the Tumour
- "It's not about my treatment doctor; I have a different question"

Our appreciation goes to all our sponsors and supporters: Cure Brain Cancer Foundation, AbbVie, Bristol-Myers Squibb, Roche, PharmAbcine, Victorian Comprehensive Cancer Centre, Ignyta, Nativis, Brainlab, BTAA, SNOG, The Ian Potter Foundation and Cancer Australia.

We hope you enjoy the ASM!

Kind regards

A/Prof Hui Gan
Convenor
COGNO ASM 2017

Professor Mark Rosenthal
Chair
COGNO

The COGNO Scientific Program has been developed independent of sponsor involvement.

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PROGRAM OF EVENTS

Sunday 22 October: Pre-ASM Meeting		
TIME	**MEETING**	**CHAIR**
12:30 - 1:30pm	**Management Committee** (closed meeting) (Phantom Room)	
2:00 - 4:00pm	**BTAA/COGNO/Olivia Newton-John Cancer Wellness Centre Patient Information Forum** (Chorus Room)	
3:00 - 5:30pm	**BCBA consortium meeting** (closed meeting) (Phantom Room)	

Monday 23 October: ASM Day 1 (Broadway Room)		
TIME	**MEETING**	**CHAIR**
8:00 - 10:00am	**COGNO Scientific Advisory Committee Meeting** (open to COGNO members only) (42nd Street Room)	Dr Liz Hovey
10:00 - 10:30am	Morning Tea	
10:30 - 10:35am	**Welcome and Day 1 program overview**	A/Prof Hui Gan
10:35 - 12:05pm	**Session 1: Tailoring Therapies for Brain Tumour - Challenges and Opportunities**	A/Prof Hui Gan
	Keyhole and endoscopic approaches for brain and skull base tumours in the era of personalized medicine: Prof Daniel Kelly	
	Tailoring Radiation Oncology: A/Prof Michael Back	
	Tailoring Drug Therapy: Prof Patrick Wen	
12:05 - 1:15pm	Lunch	
12:05 - 1:15pm	**Ignyta Lunchtime Symposium** (suitable only for clinicians and oncologists) Forging New Pathways in Targeted Therapy for Brain Tumors: The STARTRK-2 Study of Entrectinib: A/Prof Thomas John (42nd Street Room)	
1:15 - 2:15pm	**Session 2: COGNO Trials Update**	Prof Anna Nowak
	COGNO Trials: Prof Mark Rosenthal	
2:15 - 2:45pm	Afternoon tea	
2:45 - 4:45pm	**Session 3: Novel treatment strategies**	Dr Anthony Dowling
	Targeting the Immune System in Brain Tumour & Metastasis Patients: A/Prof Mustafa Khasraw	
	Targeting the Tumour Microenvironment: Dr Bryan Day	
	hTERT in glioma - a multifaceted demigod: Prof Koichi Ichimura	
6:30pm - late	**Welcome Reception and COGNO Conference Dinner** (Sea Life Melbourne Aquarium) - includes presentation of the MSD Hubert Stuerzl Memorial Educational Award and COGNO Outreach Education Preceptorship	

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Tuesday 24 October: ASM Day 2 (Broadway Room)		
TIME	**MEETING**	**CHAIR**
7:45 - 8:15am	On arrival tea/coffee	
8:15 - 8:25am	**Welcome and Day 2 program overview**	A/Prof Hui Gan
8:25 - 9:45am	**Session 4: Seeing the Target - Updates in Diagnostics and Imaging**	Dr Lawrence Cher
	Updates in Pathology: Dr Julie Lokan	
	Recent Innovations in Structural Imaging: A/Prof Frank Gaillard	
	Advanced imaging to predict response and identify pseudo progression in the NUTMEG trial: A/Prof Ben Ellingson	
	Recent Innovations in Functional and Molecular Imaging: Prof Stephen Rose	
	Q&A	
9:45 - 10:15am	Morning tea	
10:15 - 11:20am	**Session 5: Hitting the Target - Updates in Treatment**	Dr Jonathon Parkinson
	Near future neurosurgery - building upon what we do now for the decades ahead: Prof Daniel Kelly	
	Recent Innovations in Radiation Oncology: Dr Hien Le	
	Recent Innovations in Drug Development: Prof Patrick Wen	
	Q&A	
11:20 - 12:40pm	**Session 6: Research / Oral Abstracts**	Dr Jonathon Parkinson
	Can chemoprotection of the bone marrow help treat glioblastoma: A/Prof Maciej Mrugala	
	Repurposing the drug Ibudilast for the treatment of glioblastoma: A/Prof Kerrie McDonald	
	Discovery of CT-179: a small molecule inhibitor of the OLIG2 transcription factor with potent anti-tumour activity in high-grade glioma: Prof Terry Johns	
	Mimicking the biomechanical features of the brain for improved identification of effective treatments for brain cancer: Ms Victoria Prior	
	Understanding the impact of communication and language in interactions with patients with LGG: A grounded theory study: Ms Dianne Legge	
	Efficacy Analysis of Depatuxizumab mafodotin (ABT-414) +/- Temozolomide (TMZ) in Patients (Pts) With EGFR Amplified, Recurrent Glioblastoma (rGBM) From a Multicenter, International Phase 1 Clinical Trial: A/Prof Hui Gan	
12:40 - 1:15pm	Lunch	
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1:55 - 3:05pm	**Session 7: Treating the Patient, Not the Tumour**	Ms Dianne Legge
	Treatment selection in elderly patients: A/Prof Mustafa Khasraw	
	Treatment challenges in vulnerable patients: Dr Zarnie Lwin	
	"Doctor, I found this cure for brain cancer on the internet…": Dr Lawrence Cher	

Tuesday 24 October: ASM Day 2 continued		
	Interactive Panel Discussion: Tailoring Treatment for the Person in Front of You • Prof Patrick Wen • Dr Lawrence Cher • Ms Emma Daly • Ms Jane Fletcher • Dr Hien Le • Dr Brindha Shivalingam	
3:05 - 3:35pm	Afternoon tea	
3:35 - 4:50pm	**Session 8: "It's not about my treatment doctor; I have a different question"**	Ms Marcia Fleet
	"I have a legal question": Mr John Berrill	
	"I have a question about exercise and rehabilitation": Prof John Olver	
	Advance care directives / advance planning: A/Prof Brian Le	
	Q&A	
4:50 - 5:00pm	**ASM Summary and Close** (including ASM awards)	A/Prof Hui Gan

5:15 - 5:45pm	**COGNO Annual General Meeting** (open to COGNO members only)	COGNO Chair

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Session 6 **Understanding the impact of communication and language in interactions with patients with LGG: A grounded theory study**
Dianne Legge, Danette Langbecker, Patsy Yates

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Andrew B. Lassman, Martin van den Bent, Hui K. Gan, David A. Reardon, Priya Kumthekar, Nicholas Butowski, Zarnie Lwin, Tom Mikkelsen, Louis B. Nabors, Kyriakos P. Papadopoulos, Marta Penas-Prado, John Simes, Helen Wheeler, Erica Gomez, Ho-Jin Lee, Lisa Roberts-Rapp, Hao Xiong, Earle Bain, David Maag, Ryan Merrell

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PC07 **From failure to success – a retrospective audit of adjuvant glioblastoma clinical trials enrolment in tertiary referral centre**
Adrian Lee, Marina Kastelan, Helen Wheeler

PC08 **Identifying barriers to completion of adjuvant therapy in patients with newly diagnosed glioblastoma multiforme**
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PH04 **Unpacking the CARE-IS intervention: what is covered during the structured nurse-led home based support and education programme for carers of people with high grade glioma?**
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PS11 **Understanding mechanisms of IDH-mutant glioma progression and recurrence through use of latest-generation mass spectrometry**
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PS12 **A collection of primary cell line and xenograft models of proneural, classical and mesenchymal glioblastoma**
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ORAL ABSTRACTS

Mimicking the biomechanical features of the brain for improved identification of effective treatments for brain cancer

Victoria G Prior[1,2], Joey Y Vessey[1], Kaitlyn G Griffin[1], Farhana A Sarker[1,2], Tom J Grundy[1,3], Kylie Turner[1], Peta Bradbury[1], Camilla B Mitchell[1], Brett W Stringer[4,5], Bryan W Day[6,5], Terrance G Johns[7,5], Geraldine M O'Neill[1,5,3]

[1]Children's Cancer Research Unit, Kids Research Institute at the Children's Hospital at Westmead, Westmead, Australia

[2]Department of Anatomy & Histology, School of Medical Science, University of Sydney, Sydney, Australia

[3]Discipline of Paediatrics & Child Health, Faculty of Medicine, University of Sydney, Sydney, Australia

[4]Immunology in Cancer & Infection Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australia

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[7]Centre for Cancer Research, Hudson Institute of Medical Research, Clayton, Australia

Abstract

Mechanopharmacology is a recently coined term that reflects the role that the physical forces contained within tissues and organs in the body play in proliferation and invasion and, ultimately, cellular response to drugs. Seminal studies in the tissue engineering field revealed that culturing stem cells on matrices which match the softness of brain induced the cells to differentiate into neuronal lineages, independently of any other external factors. While the role for biomechanical forces has begun to be addressed in other solid cancer types, to date there has been limited consideration of this parameter in brain cancer. We hypothesized that mechanosensing (cellular sensing of mechanical forces contained within the surrounding tissue) may alter the biology and response of gliomas to anti-cancer treatments. This was tested using combinations of kinome screening and materials engineered to recapitulate the brain's soft features, together with primary patient-derived glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG) cells cultured in serum-free media to maintain in vivo characteristics. As a key feature of high grade gliomas is their propensity to migrate and invade widely throughout the brain we used time-lapse imaging and cell tracking to quantify cell migration on a range of soft brain-like matrices. This revealed that the majority of the patient lines exhibited mechanosensitive migration. Kinome screening next identified the putative therapeutic target Aurora Kinase B (AURKB) as a mechanosensitive kinase. Importantly, we have demonstrated that mechanosensitive patient lines are significantly resistant to AURKB inhibitors when cultured on soft surfaces versus plastic. Our studies suggest that the brain's biomechanical milieu is indeed an important determinant of glioma biology and response to anti-cancer treatments. We propose that assessment of the mechanopharmacology of putative treatments for gliomas should be considered as part of the preclinical assessments in the progression of novel treatments to clinical trial.

Understanding the impact of communication and language in interactions with patients with LGG: A grounded theory study

Dianne Legge[1,2], Danette Langbecker[3,2], Patsy Yates[2,4]

[1]Olivia Newton-John Cancer Wellness & Research Centre, Melbourne, Australia

[2]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

[3]The University of Queensland, Brisbane, Australia

[4]Royal Brisbane & Womens Hospital, Brisbane, Australia

Abstract

Background & Aim:

Low-grade glioma (LGG) is a relatively uncommon cancer accounting for around 15% of all gliomas diagnosed. Recent changes to LGG classification and recommended treatment regimens have resulted in a changing context for LGG. Whilst morbidity rates differ from those with high-grade glioma, the impact of diagnosis is no less significant for patients. The aim of this study was to investigate the processes by which individuals diagnosed with LGG accommodate a diagnosis of LGG into their daily lives.

Methods:

The study employed a grounded theory approach. In-depth interviews were conducted with thirteen individuals diagnosed with LGG from 3 months to 10 years post-diagnosis. Data analysis was driven by identification of social processes through coding and the use of constant comparison techniques.

Findings:

A range of social interactions contributed to the process by which people accommodated their diagnosis. In this paper, we focus on findings relating to one core theme - patient-clinician interactions and how these interactions contributed to the ambiguous clinical context associated with LGG. Findings indicate that individuals can perceive messages provided by clinicians about LGG as contradictory. These contradictory messages were reflected in statements that suggested the patient was lucky to have a LGG diagnosis. Such communication resulted in confusion, and some patients felt their concerns about the seriousness of their diagnoses were dismissed. Patients also described perceptions that information was filtered or minimised by doctors. As a result, patients sometimes experienced a lack of clarity about treatment options and prognosis.

Conclusions:

These findings reinforce the importance of understanding how communications processes are perceived by patients and the need for ongoing communications skills training for clinicians. More critically, it highlights how the use of language and contradictory terminology used by clinicians can impact individual's understanding and the way the LGG is accommodated within their life.

Efficacy Analysis of Depatuxizumab mafodotin (ABT-414) +/- Temozolomide (TMZ) in Patients (Pts) With EGFR Amplified, Recurrent Glioblastoma (rGBM) From a Multicenter, International Phase 1 Clinical Trial

Andrew B. Lassman[1], Martin van den Bent[2], Hui K. Gan[3], David A. Reardon[4], Priya Kumthekar[5], Nicholas Butowski[6], Zarnie Lwin[7], Tom Mikkelsen[8], Louis B. Nabors[9], Kyriakos P. Papadopoulos[10], Marta Penas-Prado[11], John Simes[12], Helen Wheeler[13], Erica Gomez[14], Ho-Jin Lee[14], Lisa Roberts-Rapp[14], Hao Xiong[14], Earle Bain[14], David Maag[14], Ryan Merrell[15]

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[2]Department of Neuro-Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

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Abstract

Aims: Depatuxizumab mafodotin (depatux-m), formerly called ABT-414, is an antibody-drug conjugate composed of an EGFR-directed antibody conjugated to a microtubule toxin, MMAF. Pooled safety and efficacy analysis of depatux-m +/- TMZ in EGFR amp, rGBM are reported.

Methods: In this Phase 1, open-label, multi-arm study, eligible adults (rGBM, centrally confirmed EGFR amp, KPS≥70) received 0.5-1.25mg/kg ABT-414 on days 1 and 15 +/- 150-200mg/m^2 TMZ on days 1-5 of 28-day cycles until progression (per RANO).

Results: As of 11January2017, 126 pts were treated. The most common adverse events (AEs, ≥25% pts) were ocular (90%) and included blurred vision (64%) and photophobia (31%), which were mainly reversible. Common non-ocular AEs were fatigue (36%) and headache (30%). Grade 3/4 AEs (≥5% pts) included ocular toxicities (29%) and decreased platelets/thrombocytopenia (10%). Serious AEs included seizure and keratitis (2% each). Of 125 pts evaluable by RANO, 52% had improvement or stabilization as best response (2 CR, 9 PR, 54 SD); remaining 60 (48%) had PD. Of 115 pts with measurable disease at baseline, objective response rate (ORR) was 10% (2CR + 9PR). For 5 pts, re-resection for radiographic PD revealed mostly necrotic tissue and pts were classified as SD, suggesting the ORR may be an underestimate. Of all 126 pts, the 6-month PFS rate (PFS6) was 26%; median OS was 8.5 months.

Conclusions: In this Phase 1 trial of EGFR amp, rGBM, we observed encouraging disease control (52%, CR+PR+SD) and PFS6 (26%) rates. Toxicity was mainly ocular, and reversible. A global, randomized trial of depatux-m vs. depatux-m + TMZ vs. TMZ/lomustine in EGFR amp, rGBM has completed accrual with results expected later this year (NCT02343406).

POSTER ABSTRACTS - CLINICAL

Long-term survivors of glioblastoma: A closer look

Lucy Gately[1], Sue Anne McLachlan[1], Jennifer Philip[2], Jeremy Ruben[3], Anthony Dowling[1]

[1]St Vincent's Hospital, Melbourne, Australia

[2]Centre for Palliative Care, Melbourne, Australia

[3]The Alfred Hospital, Melbourne, Australia

Abstract

Aims: Glioblastoma has a poor prognosis with median survival of 12-14 months. Long-term survivors (LTS) defined as those alive at least 2 years from diagnosis, comprise 13% of this population. This study aims to provide a clinical profile of LTS at two Melbourne institutions.

Methods: Histological diagnosis of glioblastoma from 1st January 2006 to 31st December 2012 were identified from pathology and oncology databases. Demographic, treatment and survival characteristics were recorded, with follow-up to 31st December 2015. Independent sample t-test, chi-squared and fisher exact were used to identify differences between LTS and those surviving less than 2 years. Survival estimated by Kaplan-Meier.

Results:776 patients were identified with 154 (20%) surviving >2 years. Compared with patients surviving < 2 years, LTS were more likely to be younger (median age 56 vs 65yrs, p<.001), have ECOG 0-2 (95% vs 64%, p<.001), unilateral tumours (88% vs 78%, p.004), gross tumour resection (90% vs 61%, p<.001), and receive chemoradiotherapy (69% vs 40%, p<.001).

The most common presenting symptoms amongst LTS were headache (42%), seizure (28%) and speech disturbance (16%), with 79% prescribed anticonvulsants. Of LTS, 111 patients (72%) progressed at a median of 20.1 months from diagnosis, with 46% of these undergoing a second craniotomy. Temozolomide was the most common non-surgical second line treatment (41%), followed by radiotherapy (12%). Forty percent of LTS received third line treatment, mostly chemotherapy (90%), and 10% underwent 3 or more craniotomies. The median overall survival for LTS was 38.3 months, compared with 11.0 months (entire cohort) (p<.001).

Conclusions: LTS of glioblastoma (20%) are more likely to be younger, have unilateral tumours, good performance status and undergo multimodality treatment. These data may assist in predicting LTS at diagnosis and understanding their clinical journey to facilitate planning of treatment and supportive care.

Application of the revised 2016 WHO classification of CNS tumours to a series of 82 gliomas

Te Whiti Rogers[1], Alpha Tsui[1], Michael Gonzales[1], Kathryn Field[2], Gurvinder Toor[3], Katharine Drummond[3]

[1]Department of Anatomical Pathology, Royal Melbourne Hospital, Melbourne, Australia

[2]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia

[3]Department of Neurosurgery, Royal Melbourne Hospital, Melbourne, Australia

Abstract

Introduction

Molecular features are used alongside tumour morphology in the revised WHO Classification of central nervous system (CNS) tumours. Under the new system, isocitrate dehydrogenase (IDH) mutations are used to categorise astrocytomas; diagnosis of oligodendroglioma is additionally based on co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). If molecular testing is inconclusive or unavailable, "not otherwise specified (NOS)" categories have been introduced. Here, we report the outcomes of re-classifying a series of 82 gliomas according to the new guidelines.

Methods

82 gliomas were tested for 1p/19q deletions between 2010 and 2016 using fluorescence in-situ hybridisation. Immunohistochemistry was used to test for IDH, ATRX, and p53 mutations and the 2016 classification criteria were retrospectively applied. Changes from the initial (2007) WHO classification were assessed.

Results

80 of the 82 tumours assessed could be assigned to a specific category under the 2016 classification system. Tumours originally classified as oligoastrocytoma were most commonly re-classified (Figure 1). Of 41 oligoastrocytomas; 16 were re-classified as oligodendroglioma IDH mutant, 1p/19q co-deleted; 18 as diffuse astrocytoma; 4 as anaplastic astrocytoma; and 3 as glioblastoma IDH mutant. The oligodendroglioma NOS label was applied to 2 tumours with 1p/19q co-deletion and IDH wild type. Tumours with ATRX and p53 mutations were not 1p/19q co-deleted. Co-deletion and IDH status were strongly associated with differential survival outcomes (Figure 2).

Conclusions

The use of molecular markers facilitates clinically relevant categorisation of glial tumours as astrocytoma or oligodendroglioma with improved survival correlation. A clear demarcation helps clinicians make decisions regarding optimal treatment. This is particularly relevant with the emergence of molecular targets in cancer medicine.

Figure 1

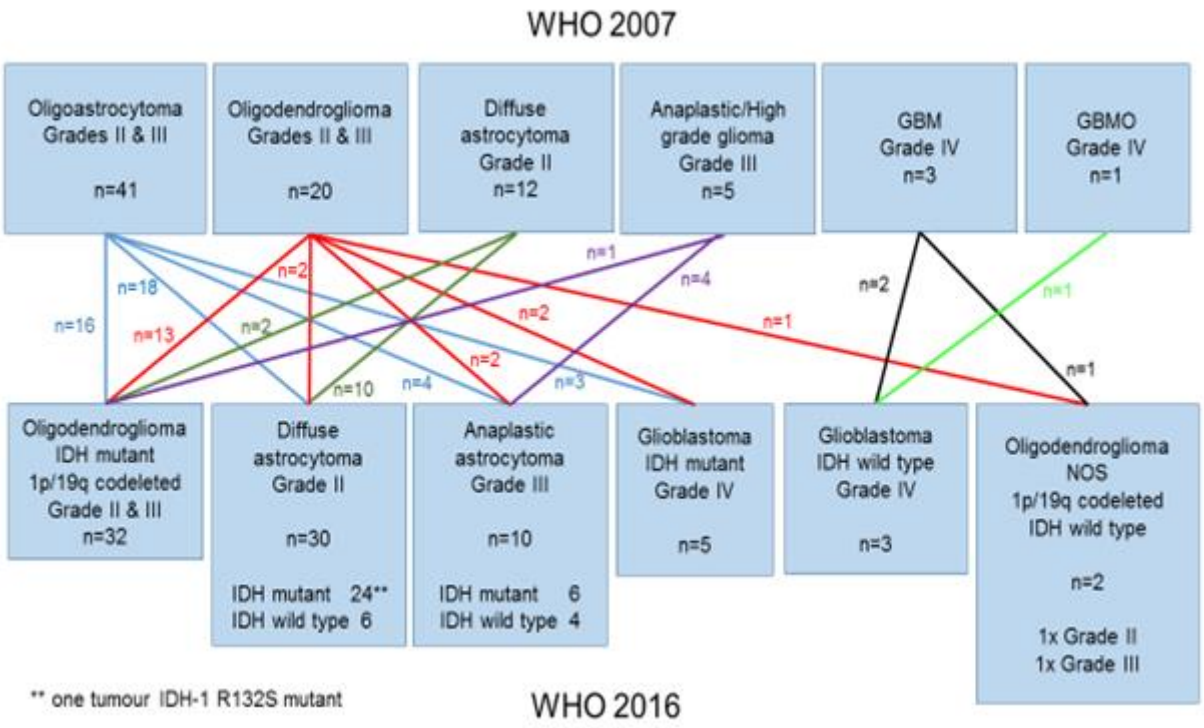
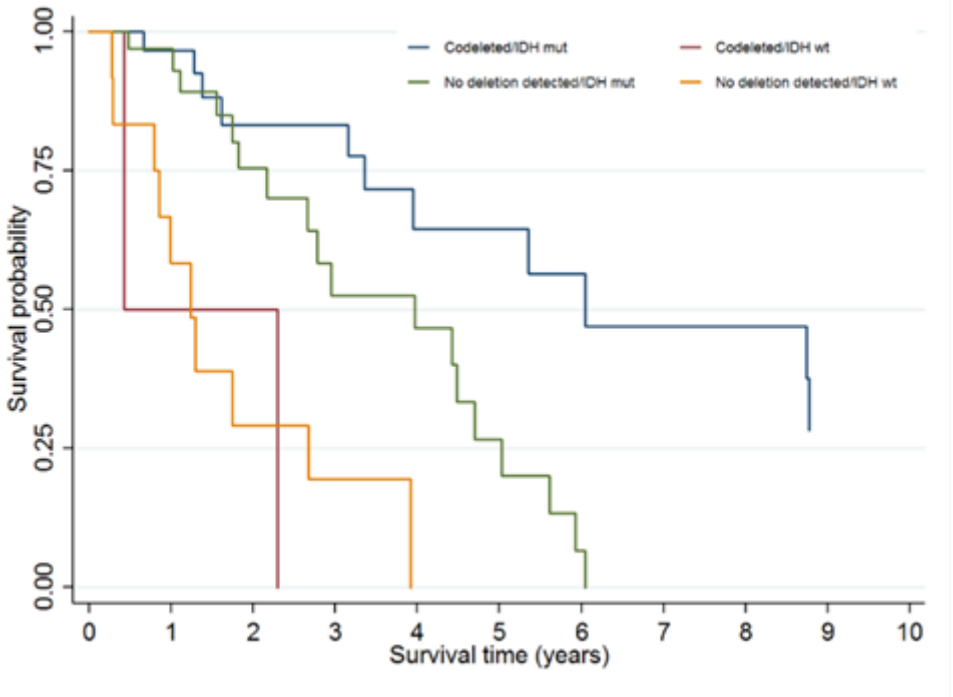


Figure 2



A multicenter, 3-arm, open-label, phase IIa clinical trial to evaluate safety and efficacy of tanibirumab (VEGFR2 mAb), in patients with recurrent GBM assessed with K-trans and Initial area under the gadolinium concentration-time curve (IAUGC)

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Abstract

Background: The VEGF signal transduction pathway is upregulated in GBM. We evaluated Tanibirumab, a mAb to VEGFR2, in an open-label, dose-escalation, 3-arm, Phase 2a clinical trial. Primary and secondary endpoints were safety and efficacy (6-month PFS, ORR, DCR and OS).

Methods: Eligibility criteria included 1st or 2nd recurrence of GBM, measurable disease,, and no prior bevacizumab. Patients were enrolled in 3 arms: Arm 1 (8mg/kg d1,8,15/q28 days); Arm 2 (12mg/kg d1,8,15/q28 days) and Arm 3 (12mg/kg weekly). Response evaluation with MRI (RANO criteria) including DCE, was performed 8 weekly.

Results: 12 patients were enrolled : 3 patients each in first 2 arms 6 in Arm 3. . Half had second recurrence.. All patients have progressed. No dose limiting toxicities (DLT) were observed. Cutaneous hemangiomas (CH) were frequent (83% of patients) and all G2 or less. No drug-related G3 or 4 AEs were observed. All SAEs were unrelated to the study drug apart from G2 bleeding haemangioma and G2 cerebral haemorrhage. Typical AEs with bevacizumab (hypertension; impaired wound healing) were not observed. No objective radiological responses occurred. 3 patients demonstrated stable disease (SD); 2 patients had SD till weeks 60 (Arm 1) & 40 (3). This was correlated with the highest expression of VEGFR2 using immunohistochemistry on archival tumour and blood vessels. Only 2 patients needed to initiate or increase corticosteroids while on treatment suggesting reduced oedema. K-trans and IAUGC showed no difference between baseline and first post-treatment scans.

Conclusions: Tanibirumab can be safely administered to patients with recurrent GBM, with CH being common. SD was seen in 2 patients up to 15 months, with some indication that tissue VEGFR2 expression may be a response biomarker. There was no correlation of response with vascular imaging. Clinical trial information: NCT03033524.

The role of 18F-fluoro-ethyl-tyrosine (FET) PET in the investigation and management of suspected low grade gliomas

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Abstract

Aims

The approach to management of low grade gliomas has changed significantly in recent years. Practice has shifted towards surgery with the aim of resection. With increasing availability of neuroimaging, clinicians are more frequently presented with lesions of unclear significance. The best management poses a dilemma.

18Fluoro-deoxyglucose (FDG) PET is used in assessment of high grade gliomas but is typically not taken up by low grade gliomas. There is increasing investigation into the utility of amino acid tracers including 18F-fluoro-ethyl-tyrosine (FET) PET. This study aims to investigate the utility of FET in low grade glioma in a single centre cohort.

Methods

Patients were identified through the Nuclear Medicine database. Patients with prior surgery or positive FDG-PET were excluded.

Patient records were reviewed to ascertain indication for imaging and management to date. PET scans were reviewed and TBRmax calculated. Histopathology results were collected. Follow up documentation and imaging were reviewed.

PET scans were assessed both qualitatively (deemed positive by a nuclear medicine specialist) and quantitatively (deemed as positive where TBRmax > 2.1.)

Results

49 patients met inclusion criteria.

20 patients had reportedly positive FET-PET, of whom 16 had histopathological diagnosis of glioma and one had response to treatment for presumed brainstem glioma. 29 patients had FET-PET reported negative and none had subsequent diagnosis of glioma.

26 patients had TBRmax>2.1, of whom 14 had confirmed glioma on histopathology. 23 patients had TBRmax< 2.1, three with subsequent diagnosis of glioma. One patient was diagnosed with stroke and the remaining 19 were stable at clinical follow up.

Conclusion

While FET-PET imaging is a useful adjunct to MRI, the FET-PET uptake below a threshold of TBRmax = 2.1 did not exclude glioma. These patients should be monitored closely for progression of their lesions.

Interim results of first-in-human study using Nativis Voyager® System in Patients with Recurrent Glioblastoma Multiforme (GBM) in Australia

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Abstract

Background: The Nativis Voyager® ulRFE® system, a non-invasive investigational device, was studied at St. Vincent Hospital Melbourne in a first-in-human feasibility study to assess safety and feasibility of the treatment for recurrent glioblastoma multiforme (GBM). The anti-mitotic therapy delivers ultra-low radio frequency energy (ulRFE) produced by changes in molecular electrostatic surface potential to the brain.

Methods: In this prospective, multi-center trial, patients with GBM, following recurrence after receiving standard-of-care chemotherapy and radiotherapy were considered for the study. Patients were treated with Voyager monotherapy. Safety was assessed by incidence of any adverse events associated with the investigational therapy. Tumor progression at 8 weeks (2 cycles) was assessed by radiological response by local site. Patients were followed at least every 8 weeks during treatment and every 4 months thereafter.

Results: Five were enrolled and treated per protocol using the Voyager A1A therapy and 11 patients were treated per protocol using the Voyager A2HU therapy. The clinical site reported two patients to be progression free after 6 cycles (24 weeks) of A1A treatment and one patient to be progression free after 6 cycles of A2HU treatment. No serious adverse events associated with the investigational therapy were reported.

Conclusions: The Nativis Voyager appears to be feasible and safe for the treatment of recurrent GBM. Given that therapy is delivered non-invasively, and no serious adverse events attributed to the investigational therapy were reported, further prospective study of the investigational device is warranted.

The hidden side of glioblastoma: one tertiary referrals experience of leptomeningeal metastases of glioblastoma

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Abstract

Leptomeningeal dissemination of high grade primary brain tumours remains a challenge to diagnose and treat with very poor prognosis once drop metastases have occurred. Symptomatic leptomeningeal metastases are not common with few reports documented. Patient outcomes remain poor despite some improvement in the overall survival of those diagnosed with glioblastoma, as survival improves; a potential increased incidence of leptomeningeal disease may be seen, however, there has been little improvement in the treatment of leptomeningeal disease over the past ten years.

Aim:

To perform an audit of those patients who were diagnosed with glioblastoma and subsequent leptomeningeal spread treated via Royal North Shore Hospital (RNSH) campus between 2008 and 2017. We aim to document incidence of leptomeningeal disease, relationship to site of primary disease, patients survival post leptomeningeal diagnosis and time to occurrence post initial resection.

Method:

We have done a retrospective audit of patients with primary glioblastoma referred to our institution between 2008 - 2017 & identified those who developed leptomeningeal disease. We have correlated this with the site of primary resection, treatment and other glioblastoma prognostic indicators. The cohort included those with a definitive diagnosis (Lumbar Puncture and imaging) or symptoms highly suggestive of leptomeningeal spread. With the introduction of Bevacizumab, definitive imaging poses further diagnostic challenges.

Results:

Symptoms, diagnostics, procedures, management and outcome will be presented.

Conclusion:

In summary, with increasing treatment options & increased survival, the incidence of leptomeningeal spread may pose diagnostic and management challenges which will need further investigation.

From failure to success – a retrospective audit of adjuvant glioblastoma clinical trials enrolment in tertiary referral centre

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Abstract

Clinical trial participation is often viewed as the gold standard of care in many oncology patients. This is particularly true in areas like Glioblastoma where there is a poverty of options. Trial enrolment enables patients to gain access to new restricted therapeutic agents. Patients (and their families) often very actively seek out trial centres with great anticipation. However, not all enrolments end in successful trial participation and some will be rejected with disappointment.

Aim:

To perform an audit of adjuvant glioblastoma clinical trials enrolment at Royal North Shore Hospital (RNSH) campus and to identify barriers to trials participation and factors involved with enrolment rejection (screen failures).

Method:

We have searched retrospectively in our neuro-oncology database and trials screen logs between 2015-current to identify all newly diagnosed glioblastoma patients treated at our campus. Data on demographics, ECOG, co-morbidities, geographical location, reasons for rejection, and ineligibility factors were documented. Collected data will be analysed descriptively and presented at completion.

Results:

From 2015 to current, 120 new glioblastoma patients were managed through RNSH campus. 48 patients were screened for clinical trials. 24 patients fulfilled eligibility criteria and enrolled and participated in adjuvant glioblastoma clinical trials. 12 patients screened for multiple trials. Further data collection will highlight the difficulties in trials recruitment and factors leading to screen failure. Factors contributing to screen failure will include: lack of molecular target, patient preference, technical issues, and declining performance statuses.

Conclusion:

In summary, clinical trials participation for glioblastoma patients remain low despite it being recognised as a gold standard in clinical oncology care currently. Furthermore, additional clinicopathological factors further reduce trials participation rates. Adaptive clinical trials strategies will be needed to improve recruitment in the future.

Identifying barriers to completion of adjuvant therapy in patients with newly diagnosed glioblastoma multiforme

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Abstract

Glioblastoma multiforme (GBM) are the most common and aggressive primary brain tumours diagnosed in adults and despite aggressive therapy, prognosis is dismal. The Stupp protocol is the standard therapy for GBM and, compared to radiation alone, offers an increase in 2-year survival rate with no significant associated impairments. However, it has been found that only 2/3 of medically eligible GBM patients in Toronto, Ontario successfully complete adjuvant therapy. This raises questions about the factors influencing treatment decisions, indicating that there may be other underlying barriers preventing treatment completion in this population. While several studies have looked at quality of life, few have addressed patients' perspectives on health related quality of life (HRQOL) in their treatment decisions and how they can be used to improve the support provided by healthcare personnel in this process. Therefore, a mixed methods approach, which explores patient's perspectives on the treatment decision-making process and the factors that influence the process, is warranted. With the aid of both quantitative and qualitative measures, we aim to explore factors influencing treatment decisions so as to identify these barriers in order to promote improved patient-centered care. We plan to canvas 250 newly diagnosed GBM patients prospectively. Clinical and demographic data will be collected for all participants. Patients undergoing the Stupp protocol will complete the HRQOL questionnaire and a subgroup of these patients will undergo a series of interviews throughout treatment. The results of this study will provide a comprehensive overview of the barriers influencing a GBM patient to discontinue treatment and may help to inform the shared decision making process between the oncologist, patient, caregivers, and healthcare team. This may highlight areas in the process requiring additional attention in order to alleviate some of these barriers in the hopes of helping more patients reach treatment completion.

POSTER ABSTRACTS - HOLISTIC CARE

Prevalence and severity of difficulty sleeping in CNS cancer patients in Australia

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Abstract

Background: Insomnia is one of the most distressing symptoms in cancer patients, including central nervous system(CNS) cancers. It can negatively influence treatment outcomes, physical and emotional health, and quality of life. Unfortunately, there has been little attempt to systematically screen, assess and manage sleep difficulties.

Aims: The present study aimed to establish the scope of the problem of difficulty sleeping in patients with CNS cancer. It aimed to establish the longitudinal trajectory of difficulty sleeping at different levels of care (e.g. patient, care phase and episode) and care settings (inpatient or community), and to identify clinically modifiable predictors of difficulty sleeping in cancer supportive care.

Methods: A cohort of 2406 patients with CNS cancer who received palliative care at a Palliative Care Outcomes Collaboration (PCOC) participating centre in Australia from 2010 to 2015 were included. Patients were evaluated on patient-reported and clinician-rated outcomes at the start and end of a care phase in their routine care. Four types of care phases (e.g., stable, unstable, deteriorating, or terminal) described a distinctive clinical status and care needs of a patient and constituted a care episode in a single centre or care setting.

Results: There were 8897 care phases comprising 3310 care episodes, and 53.6% of patients received inpatient care. The most common phase type was deteriorating (36.6%). Patients were significantly younger than the general palliative care population in Australia (46.1% at age of <65). Reporting of difficulty sleeping was most prevalent at the start of unstable phase (40.9%) followed by the start of deteriorating phase (Fig. 1). Sleep scores fluctuated greatly even within an individual patient.

Conclusion: Our preliminary findings indicate a high prevalence and longitudinal fluctuations in sleep difficulty. Further analyses will demonstrate relationships of sleep with changes in the patient's clinical status and with care settings, and its clinical predictors.

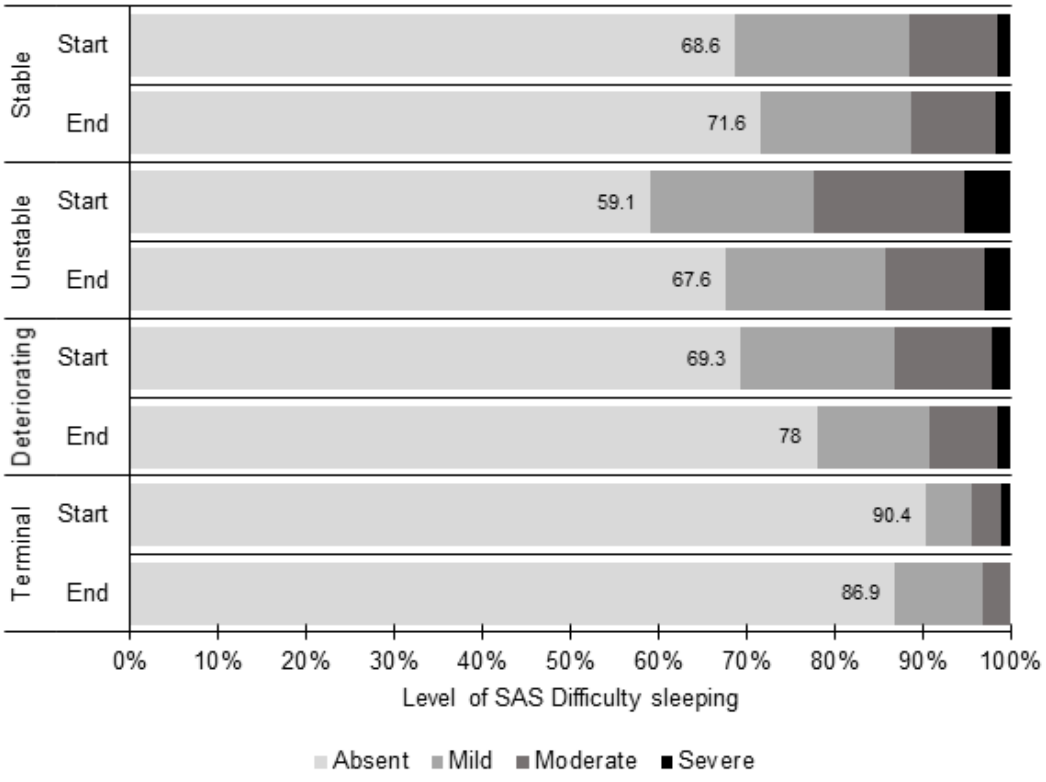

Fig 1. Severity outcome of difficulty sleeping at the beginning and end of each phase type

The development of a framework for Supportive and Palliative Care for patients with high grade glioma and their family caregivers

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Abstract

Patients with high-grade malignant glioma (HGG) have significant supportive and palliative care needs yet few tailored guidelines exist to inform practice.

Aims: This study sought to develop a HGG framework of supportive and palliative care informed by patient, family and health care professional (HCP) reported needs.

Methods: This study integrates a program of work consisting of a series of mixed-methods studies including: (1) Qualitative study: exploring experiences through systematic literature review and qualitative interviews (10 patients, 23 carers and 36 HCPs); (2) Epidemiological cohort study (N=1,821) describing care of incident cases of HGG in Victoria, Australia using linked hospital datasets. A multidisciplinary expert advisory committee was convened to consider the findings of (1) and (2), and develop a framework of supportive and palliative care across the illness course based on the findings of (1) and (2).

Results: A series of key principles guiding framework development were established, including that care: (1) aligns with patient/family caregiver needs according to illness transition points; (2) involves continuous monitoring of patient/family caregiver needs; (3) be proactive in response to anticipated concerns; (4) includes routine bereavement support; and (5) involves appropriate partnership with patients/families. Activities aligned with these principles and designed to address unmet needs were enacted at illness transition points and included : Co-ordination, repeated assessment, staged information provision according to the illness transition, proactive responses and referral systems, and specific regular enquiry of patient's and family caregivers' concerns .

Conclusion: This framework of supportive and palliative care, informed by evidence, provides an approach for patients with HGG that is responsive, relevant and sustainable. Future research to evaluate this conceptual framework in controlled clinical trials is now required.

Participating in exercise during chemoradiotherapy helps patients diagnosed with High Grade Glioma to feel stronger and actively involved in their fight against cancer: a qualitative study

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Abstract

Introduction: While exercise has been demonstrated to improve physical function and wellbeing in people with other cancer diagnoses, no research has examined the potential impact of exercise for HGG patients.

Aim: To describe HGG patients' and carers' perspectives of the benefits and challenges of participating in a tailored exercise intervention during chemoradiotherapy.

Methods: Patients with HGG undergoing chemoradiotherapy received a supervised exercise intervention involving an individualized prescription of moderate intensity aerobic and resistance exercise twice weekly, performed at the hospital when they attended for treatment. Semi-structured interviews were conducted with participants and their carers to understand their perspectives about the program. Recordings were transcribed and analysed using content analysis.

Results: 19 patients and 15 carers were interviewed. The following themes emerged: individually tailored exercise, keeping active, regaining a sense of control, commitment to the program, enjoying exercise again, interacting with people, scheduling exercise into routine and continuing exercise beyond the program. Overall, the exercise program was enjoyed by patients, helped them to feel stronger, enabled them to feel a sense of control and achievement and involved in the fight against their cancer. Although patients were experiencing significant symptoms and side effects including fatigue they were able to continue to participate in the program because it was tailored to how they were feeling each time they attended. Carers were also supportive of the program, highlighting that it improved how the patients were feeling physically and mentally and it also provided them with a much needed break from full-time caring.

Conclusion: Patients and carers expressed positive perceptions and experiences of participating in exercise during chemoradiotherapy. These results support the quantitative pilot study which demonstrated that supervised exercise is feasible, safe and well tolerated by patients receiving chemoradiotherapy for HGG. Randomised controlled trials now need to be conducted with this population.

Unpacking the CARE-IS intervention: what is covered during the structured nurse-led home based support and education programme for carers of people with high grade glioma?

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Abstract

People with High grade glioma (HGG) have high care needs. Their carers experience distress and feel inadequately prepared for their role.

Aims: The CARE-IS randomised controlled trial (RCT) aims to evaluate a nurse-led education and support program to improve carer preparedness, improve their quality of life; reduce anxiety and depression; and decrease unplanned use of health services. In this presentation we will describe the areas identified in which carers require assistance and the types of referrals that are being made.

Methods: Randomised, controlled, unblinded Phase III trial comparing usual care with the intervention. The carer intervention consists of 1) Telephone assessment of carer's needs; 2) Nurse-led home visit; 3) Personalised resource file individually tailored and 4) ongoing telephone support for 12 months. Telephone assessments were recorded, transcribed and analysed using content analysis.

Results: To date, 52 carers have received the intervention. Recordings of the nurse-led telephone assessments of carer's needs were analysed. Analysis highlighted the complexity of the experience of caring for someone with HGG. The nurse developed rapport and worked with carers to identify problems in these areas: caring for yourself (e.g. anxiety, carer strain/burden); practical matters (e.g. occupational therapy, legal advice, transport); communication; treatment; physical symptoms; mental and behaviour changes; fertility and sexuality; lifestyle choices and end of life care. After identifying problem areas the nurse provided tailored education and support and when necessary made appropriate referrals. Further details will be presented.

Conclusions: Carers needs assessment provided an understanding of their specific problems. These problems are unlikely to be addressed during usual care because the focus is on treating the patient with HGG and symptom control rather than addressing carer needs. This RCT will demonstrate whether the nurse-led intervention is effective in reducing carer distress and improving carer outcomes.

Safety and feasibility of supervised exercise during adjuvant treatment of high-grade glioma

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Abstract

Aims. Patients with high-grade glioma (HGG) are treated with surgery followed by chemoradiotherapy; dexamethasone is a common supportive care medication. Treatment and supportive care may result in deconditioning and adverse changes in body composition. Exercise may be an effective intervention to maintain or improve function and body composition, but no previous research has examined the potential impact of exercise during chemoradiotherapy. We aimed to evaluate if exercise was feasible and safe in patients with HGG undergoing chemoradiotherapy.

Methods. 29 patients (69% men; 52±12 years) with HGG scheduled to receive chemoradiotherapy participated in this pilot study. Patients self-selected to receive either usual care (n=5) or a supervised exercise intervention (n=24) throughout chemoradiotherapy. The intervention involved an individualised prescription of moderate-intensity aerobic and resistance exercise during twice weekly sessions at the hospital. Assessment of quality of life (QOL), fatigue, distress, physical function and body composition were conducted ≤10 days before and following chemoradiotherapy.

Results. Four (14%) participants withdrew; baseline characteristics did not differ significantly from non-withdrawers (p≤0.05). Exercise session attendance was ~80±4%; one adverse event relating to the intervention was reported. The intervention improved function but few other changes were observed. Changes were influenced by whether participants were receiving dexamethasone. Function significantly improved while QOL and symptoms did not worsen in exercising patients not receiving dexamethasone. Patients receiving dexamethasone significantly decreased QOL, increased fat mass and did not improve function despite exercising. Too few participants self-selected usual care to allow a detailed understanding of changes during chemoradiotherapy in patients not undertaking exercise.

Conclusions. Supervised exercise is safe and well tolerated by HGG patients undergoing chemoradiotherapy. Outcomes following exercise were better in those not receiving dexamethasone. Randomised controlled trials are required to further explore these findings.

The Australian Adolescents and Young Adults (AYAs) Pattern of care (POC) study-Central Nervous System Cancers Survival Update

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Abstract

Aims: We have previously described the management of a retrospective Australian cohort of AYAs with CNS tumours treated over a 6 year period and now present the overall survival data.

Methods: 270 15-24 year-olds diagnosed with CNS malignancy between 1/1/2007 and 31/12/2012 were identified through population-based cancer registries (4 states) or hospital medical records. Survival data was provided by the National Death Index at the AIHW with data cut-off 1 November 2016.

Overall 5 year survival for the cohort was 70% (95% CI 64-75%). Survival was influenced by tumour subtype (Table 1) but not by treatment type (surgery, chemotherapy, radiotherapy or a combination). The trend towards excess male to female incidence was also noted in the Australian population but unlike some studies the survival rate was not significantly influenced by sex p=.620). Numbers precluded assessment of survival by type of treatment centre (paediatric versus adult) or location (regional versus metropolitan). Only 14 out of 270 patients participated in a clinical trial.

Table 1. CNS tumour subtypes and survival

	1 year survival % (CI %)	5 year survival (CI%)	Of those who were deceased, number of *months* survived	
			Median	Range
Low grade glioma	98 (94-100%)	86 (78-91%)	41	1-107
High grade glioma*	81 (70-88%)	43 (31-53%)	16	0-75
Medulloblastoma/PNET	94 (78-98%)	60 (41-74%)	18	7-52
Ependymoma	95 (68-99%)	89 (64-97%)	11	6-16
TOTAL	**92 (88-95%)**	**70 (64-75%)**		

Conclusions: Outcomes are lower compared to a population study of a similar era in the UK [1]. Results do not show improvement in 5 year mortality trends for this Australian cohort compared to historical survival rates, despite an annual improvement in AYA cancer mortality of 1.9% between 1983 and 2007.[2]

Life beyond a diagnosis of glioblastoma: A systematic review of the literature

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Abstract

Aims: The median survival of glioblastoma is 12-14 months with approximately 13% of all patients diagnosed surviving at least 2 years from diagnosis. Patients diagnosed with glioblastoma face poor prognosis, significant symptom burden and high care needs. The aim of this study is to undertake a literature review to document the issues encountered by long-term survivors of glioblastoma, a small but important subset of patients.

Methods: MEDLINE, PsychInfo and EMBASE were searched with core concepts: (1) glioblastoma, (2) survivor and (3) terms pertaining to survivorship issues. Following a PRISMA strategy, a thematic analysis was undertaken of the three included studies.

Results: Themes are outlined in Table 1. Long-term survivors of glioblastoma encounter neurologic deficits, impairment in cognition, psychological distress, reduced social function and future uncertainty. These issues may result in difficulties living independently, the inability to return to work and financial difficulties. Independence in activities of daily living, working memory and overall quality of life appear to be preserved in the majority.

Conclusions: Long-term survivors of glioblastoma continue to have significant symptom burden and care needs, with a relatively preserved patient-reported quality of life. Overall, there is currently a paucity of literature surrounding this topic. Further research focusing upon qualitative testing and improving detection of issues is required to accurately describe these issues. This will allow for improved supportive care to be implemented in the community and the outpatient setting.

Table 1: Themes emerging from literature

FUNCTIONAL INDEPENDENCE	NEUROCOGNITIVE	PSYCHOLOGICAL WELLBEING	PATIENT REPORTED QUALITY OF LIFE
Neurologic deficits are common and impact on a patient's ability to live independently. A significant proportion is unable to work.	Cognitive deficits are present in the majority of patients.	Psychological symptoms and distress present in 1/3 of patients.	Appears unaffected. Fatigue, financial difficulties and future uncertainty are common. Social functioning and role functioning reduced.

Health-related quality of life and cognition post-resection of benign brain tumours

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Abstract

Introduction

Surgery is a mainstay in the management of intracranial neoplasms including acoustic neuroma (AN), meningioma, and low grade glioma (LGG). These patients have long periods of survivorship following resection. The quality of this survival is as important as its duration. Health-related quality of life (HRQoL) is a self-reported measure of this quality. Cognitive dysfunction is often reported by the patients in this population and is known to impact HRQoL. We aim here to investigate HRQoL and cognition in a population representative of that seen in an outpatient neuro-oncology service.

Methods

428 English speaking adult participants were recruited from neurosurgical outpatient clinics. HRQoL assessment was performed using the EORTC's QLQ-C30 and QLQ-BN20 surveys. Cognition was assessed using Folstein's MMSE in 264 participants and a novel brain tumour specific cognitive battery was piloted in a group of 27 participants.

Results

Participants reported significant HRQoL and functional impairment relative to a reference population (Figure 1). This impairment remained stable over a modest followup period. Fatigue was the symptom most associated with impaired HRQoL across tumour types. Functionally, the largest degree of impairment was reported in the cognitive and social domains. Performance on MMSE did not correspond with perceived cognitive function. Impairment was noted on tasks assessing processing speed and working memory. A closer association was seen between computerised battery performance and perceived function; however, significantly discordant results were also common (Figure 2).

Conclusions

People treated for benign brain tumours have poorer HRQoL than healthy controls. Fatigue is the symptom most associated with impaired HRQoL. Functionally, there is prominent self-reported cognitive and social impairment.

The discord between objective assessment and self-reported perception of cognitive function warrants further investigation and may allow therapeutic interventions.

Figure 1 - *P<0.05. **P<0.01

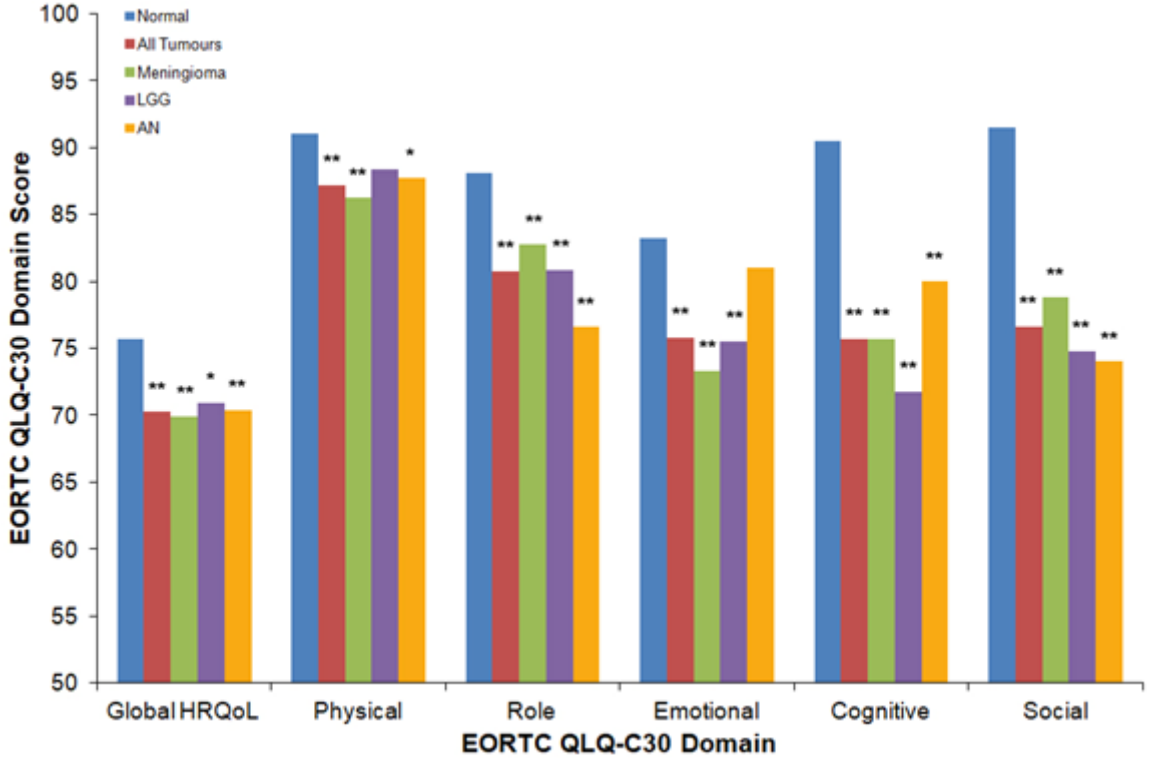
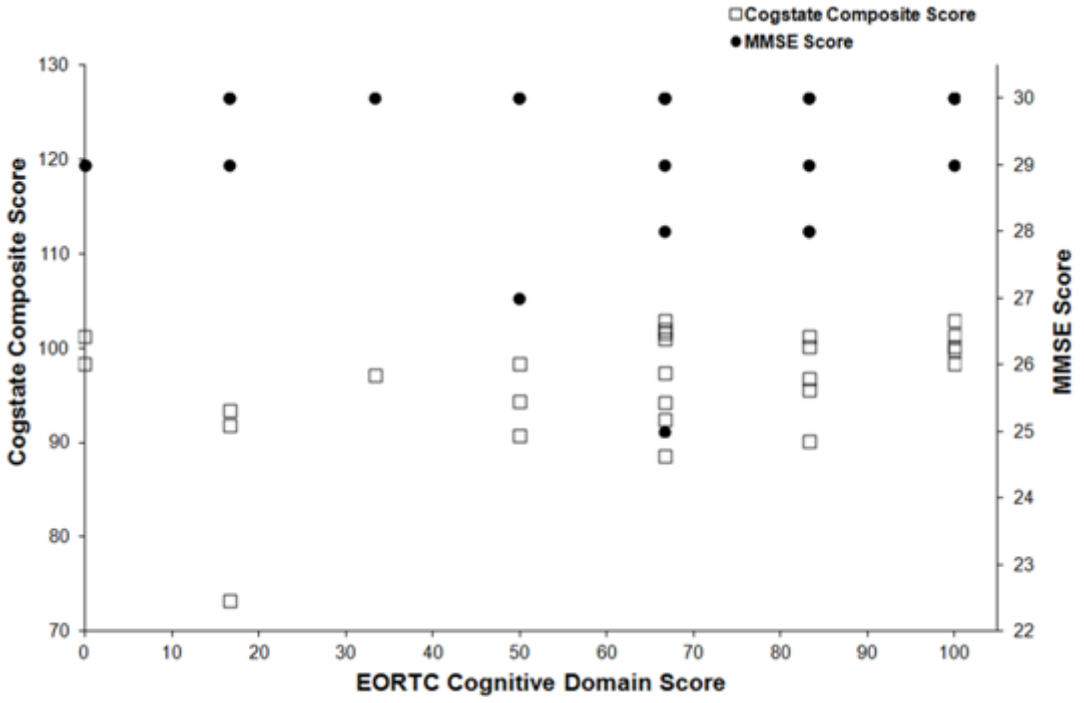


Figure 2



POSTER ABSTRACTS - SCIENCE

Roles of ATRX and histone variant H3.3 in gliomagenesis

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Abstract

Histone variant H3.3 and its chaperone ATRX are frequently mutated in cancers including gliomas. Here we investigate chromatin defects and DNA instability associated with H3.3 mutation (a G34R substitution) and ATRX knockout.

Ribosomal RNA gene (rDNA) instability is a hallmark of cancers. Here we report a loss of chromatin maintenance and instability at rDNA repeats in ATRX knockout cells, accompanied with altered RNA Polymerase I (Pol I) transcription. We propose that loss of ATRX contributes to the de-regulation of rDNA chromatin in cancers. In the absence of ATRX, the disrupted chromatin organisation and DNA integrity in the rDNA clusters could allow for selection of cell populations that have amplified their rDNA complement, hence, promoting rRNA production for rapidly dividing cancer cells. Supporting this, rDNA repeats display extensive DNA rearrangement and amplification in ATRX-mutated human ALT (Alternative Lengthening of Telomeres) cancers. We will discuss the potential Pol I inhibition for treatment of ATRX-mutated cancers including glioma.

We introduced a single-copy H3.3 G34R mutation in ESCs. The expression of H3.3 G34R mutant was found to drive increases in H3K36me3 and H3K9me3 across the genome. We will discuss the effect of H3.3 G34R on H3K9 and K36 demethylation. Our study illustrates that histone point mutations can exert a whole-genome effect to promote glioma formation.

Determining how FUBP1 drives Oligodendroglioma to develop novel treatment strategies

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Abstract

The best-case scenario for Oligodendroglioma patients is a prolonged disease (>15 years) associated with significant morbidity (including seizures and neurological deficits). More alarming are recent observations that standard of care therapies can actually cause a subset of these oligodendrial tumours (around 15%) to become extremely aggressive to rapidly cause mortality. The reasons for this are unclear, but current histopathological classification methods do not reliably predict response to treatment. Thus, new molecular prognostic markers to personalise treatments are imperative if we are to increase outcomes for Oligodendroglioma patients.

FUBP1 ranks in the top 10% of driver mutations in primary Oligodendrial brain cancers (The Cancer Genome Atlas (TCGA)). However, Oligodendroglioma genetics is complex, with several frequently identified driver mutations (e.g. CIC, NOTCH1, PIK3R1/PI3KCA, EPC2, HDAC2) co-occurring with FUBP1. As the consequence of these mutant combinations to tumour behaviour is unknown, we have set out to determine how specific Oligodendroglioma genotypes correlate with tumour progression. To clearly connect genotype and phenotype in the glial cells that drive primary brain cancer, we have developed genetically tractable in vivo systems (Drosophila and mouse). Importantly these systems have signalling cues essential for brain development intact. Moreover, in accordance with the identified tumour suppressor function, we have demonstrated that FUBP1 is essential for inhibition of glial lineage proliferation in the mouse and Drosophila brain. Thus, we aim to use this unique toolkit to determine how FUBP1, and the network of co-occurring mutations, alter glial lineage proliferation and glioma progression. Such information on how these molecular markers impact glioma biology are essential to improve predictions regarding tumour aggression and response to therapy. Further to providing prognostic markers to guide treatment using current drug therapies, we are working to determine efficacy of small molecules targeting the FUBP-axis, to open new avenues for glioma treatment to ultimately improve patient outcomes.

Small Animal Radiation Research Platform (SARRP): Aiding the optimisation of combined therapy for brain cancer

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Abstract

Aims: To advance pre-clinical assessment of existing and novel combined therapies for brain cancer we have acquired the Small Animal Radiation Research Platform (SARRP; Xstrahl, USA). The Gl261-Fluc mouse glioma model can be used to assess the inflammatory response to brain cancer, surgical resection, radiation therapy, chemotherapy, and checkpoint inhibitor immunotherapy.

Methods: The SARRP uses orthovoltage X-ray radiation for 3D cone-beam computed tomography (CBCT) and bioluminescent tomography (BLT) image-guided radiation therapy of small animals. Focal radiation of a 0.5 mm diameter circle to whole body irradiation can be applied in fixed or dynamic X, Y, Z, θ (360°) planes to replicate conformal patient dosing. Mice implanted with Gl261-Fluc cells are treated on day 10 with combined therapy. For example, 2Gy/day X-ray radiation for 5days, 200 mg/m^2/day Temozolomide for 5days, and 10mg/kg anti-PD-1 mAb every 2 weeks to mimic patient regimens.

Results: The SARRP and BLT (MuriGlo®) unit are shown in Figure 1. We are also developing a biopsy and surgical resection method to complete the model for all treatment modalities currently available to patients. We expect to utilise this mouse glioma model and the SARRP to advance knowledge of the tumour microenvironment and inflammatory response to cancer; optimise and tailor therapies for brain cancer; and to develop treatment regimens that minimise tissue damage and immune-related adverse events to combined therapy, which are associated with poorer patient outcomes.

Conclusions: The SARRP is an integral piece of pre-clinical research technology to aid in the development of combined therapy for brain cancer and guide clinical trial protocols. Incorporation into a research pipeline will accelerate preclinical studies to improve the cancer experience, quality of life, and survival of patients.

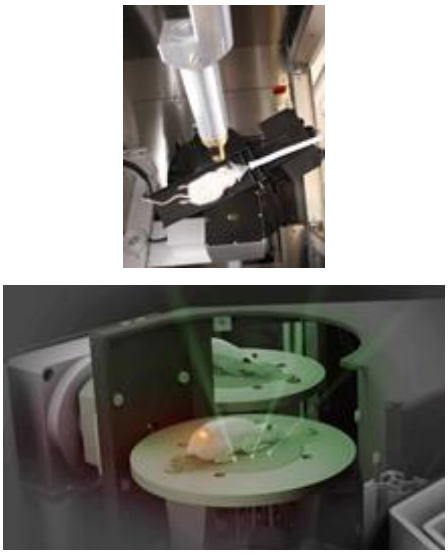

Figure 1. Images of the SARRP (right) and BLT unit (MuriGlo®; left) reproduced with permission from © 2017 Xstrahl Limited – All Rights Reserved.

Serum exosomes in glioblastoma patients: an opportunity for non-invasive diagnosis and monitoring

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Abstract

Surrogate endpoints are increasingly important in clinical trials, enabling faster regulatory approvals for therapeutics in diseases with poor outcome, and assisting in the new generation of adaptive clinical trial design. Exosomes are nano-sized extracellular vesicles shed by cells of all types, and their release is upregulated in pathological conditions. Exosomes can traverse the blood-brain barrier, and brain tumour exosomes have previously been found in the blood. Exosomes encapsulate a molecular cargo that is typical of their cell of origin. The promise of exosomal miRNA as a GBM biomarker has recently been demonstrated in two studies that have reported changes in serum EV miRNA composition in GBM patient sera. However these studies examined only a small number of patients at only handful of miRNA.

With emerging technology it is now feasible to perform an unbiased assessment of all exosomal miRNA from any cell type. We have successfully optimised serum exosome purification and RNA isolation protocols, as well as unbiased deep sequencing and downstream bioinformatics analysis in our pilot study of eight GBM patients and matched controls. This has identified numerous (>30) serum exosomal miRNAs with significant differential expression between controls and GBM. We are now analysing selected samples from the VERTU GBM clinical trial, with the hope of identifying an exosomal miRNA signature of GBM disease activity. This may be a valuable surrogate endpoint marker for future clinical trials, as well as assisting in future clinical management of patients with GBM.

A custom glioma-specific deep sequencing panel for accurate brain tumour diagnosis

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Abstract

Modern brain tumour classification now requires a layer of molecular data to supplement histological diagnosis and tumour grading. In addition, characterisation of molecular alterations for patient enrolment into modern clinical trials often requires molecular data over and above what is currently mandated in the 2016 WHO classification. To address these issues, we have adapted a custom glioma-specific deep sequencing panel for comprehensive brain tumour characterisation. This assay, modified from a panel detailed by our International Neuropathology colleagues(1), assesses somatic mutations and copy number changes in 20 genes that are frequently altered in different glioma subtypes (e.g. IDH1/2, ATRX, TP53, BRAF, H3.3, TERT). This new test also simultaneously assesses copy number changes for whole chromosomal arms on chromosomes 1, 19, 7 and 10, and other specific copy number changes such as EGFRvIII variant and the BRAF/KIAA1549 fusion/duplication event. Importantly, only 20 ng of input DNA is required, making this assay ideal for small brain biopsy specimens. Here we present the results of our assay panel validation exercises, and detail the spectrum of molecular alterations seen in a cohort of glioma patients (n=20). The implementation of this custom glioma-specific molecular panel in a NATA-accredited clinical diagnostic environment will not only serve to refine tumour classification for patient management and clinical trial enrolments, but will be an important step towards a 'personalised treatment' platform for brain tumour patients.

Reference: (1) Zacher A,…..,Reifenberger G. (2017) "Molecular Diagnostics of Gliomas Using Next Generation Sequencing of a Glioma-Tailored Gene Panel." Brain Pathol.;**27(2)**:146-159

Identifying the therapeutic role of histone deacetylase inhibitors on paediatric tumours

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Abstract

Introduction: Atypical teratoid rhabdoid tumors (AT/RT) and Malignant Rhabdoid Tumour (MRT) are aggressive and undifferentiated tumours primarily affecting the brain, lungs and kidneys of infants. Current treatments are ineffective and cause adverse side effects due to their lack of selectivity for cancer cells over non-cancerous cells. Therefore, identification of alternative treatment options is needed.

Aims: The study's objective is to investigate the cytotoxicity of pan-histone deacetylase inhibitor (pan-HDACi) and selective-HDACi on AT/RT and MRT cells.

Materials and Methods: AT/RT cell lines, BT-12 and CHLA-266, MRT cell line, G401, and normal kidney cell line, HEK293T, were used to investigate the therapeutic activity of HDACi. Cells were treated with either pan-HDACi, Panobinostat, or selective-HDACi, Romidepsin, Abexinostat or CUDC-907 at increasing concentrations (1nM - 1μM) for 24, 48 and 72 hours. Cell viability was assessed using MTT assay and the growth inhibition by 50% (GI50) was calculated.

Results: Cell viability profiles across all cell lines showed cancer cells were more sensitive to HDACi treatments as compared to normal cells. Panobinostat induced significant GI50 at 50nM, 282nM, and 192nM at 48 hours for G401, BT-12 and CHLA-206 cell lines respectively. In addition, selective-HDACi, CUDC-907 was found to be more potent than Panobinostat, with GI50 being achieved with 13nM, 70nM and 67nM within 48 hours on G401, BT-12 and CHLA-206 cell lines respectively. Interestingly, GI50 of HEK293T normal cells were only observed after 72 hours at very high concentrations of Panobinostat (500nM) and CUCD- 907 (424nM).

Conclusion: Taken together, these results show that HDACis are sufficient in inhibiting the growth of AT/RT and MRT cells and hold great potential as alternative anticancer therapies due to their ability to preferentially target cancer cells over normal cells.

Targeting brain cancer metastases – a double targeted strategy for effective drug delivery

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Abstract

Aims: Brain metastases occur in up to a quarter of all cancer patients following primary malignancy treatment, and the prognosis for these patients is very poor. The treatment of these metastatic tumours is greatly hindered by the presence of the blood brain barrier (BBB) which restricts the overwhelming majority of small molecules from entering the brain. A novel approach to overcome this is to target receptor mediated transport mechanisms present on the endothelial cell membranes, in particular the transferrin receptor. Given their specificity, safety profile and stability, nucleic acid based therapeutics are ideal for this purpose.

Methods: An aptamer targeting the transferrin receptor was fused with an aptamer that binds to a cell surface marker on breast cancer cells, the epithelial cell adhesion molecule (EpCAM), enhancing binding affinity of both aptamers while maintaining specificity, and confirmed through flow cytometry and confocal microscopy.

Results: Using an in vitro BBB model, the aptamer transcytosed the barrier and targeted only EpCAM positive cells in a co-culture of EpCAM positive and negative cell. This aptamer also specifically delivered doxorubicin across the in vitro BBB in a timely manner. In vivo, we confirmed the aptamer's ability to transcytose the BBB in a healthy mouse model following a single i.v. injection (40 nmol/kg)[1], and in an animal model of breast cancer brain metastases.

Conclusions: These promising results demonstrate that through the fusion of two aptamer sequences, a bi-functional aptamer can be generated which has the potential to be developed for the specific treatment of EpCAM positive brain metastases.

References

[1] J Macdonald, J Henri, L Goodman, D Xiang, W Duan, S Shigdar. Development of a Bifunctional Aptamer Targeting the Transferrin Receptor and Epithelial Cell Adhesion Molecule (EpCAM) for the Treatment of Brain Cancer Metastases. *ACS Chemical Neuroscience* **2017** 8 (4), 777-784.

Analysis of pre and post treatment glioblastoma demonstrates changes in APE1, a DNA repair enzyme, and the tumour associated macrophage signature

Amanda Hudson[1,2,3], Nicole Parker[1,2,3], Peter Khong[1,2,3], Jonathon Parkinson[1,2,3], Rowan Ikin[1,2,3], Ying Zhu[4,2,3,5], Jason Chen[6,2], Helen Wheeler[1,2,3], Viive Howell[1,2,3]

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Abstract

Introduction and Aim: Glioblastoma, the most common and aggressive brain cancer in adults, has a very grim prognosis and a 5 year survival rate of less than 10%. While treatment with surgery, radiotherapy and/or chemotherapy may prolong life, progression is inevitable. What is still unknown however, is how much these treatments and progression of disease affect the molecular profiles of these tumours and how these tumours adapt to withstand these treatment pressures. Understanding such changes will uncover pathways used by the tumour to evade destruction and will elucidate new targets for treatment development.

Method: Nineteen matched pre-treatment and post-treatment glioblastoma tumours were subjected to gene expression profiling (Fluidigm, TaqMan assays), MGMT promoter methylation analysis (pyrosequencing), targeted next generation sequencing and protein expression analysis (immunohistochemistry).

Results: Relative to pre-treatment specimens, post-treatment specimens had molecular changes which correlated with known resistance mechanisms including increased expression of APE1 ($p<0.05$) and altered MGMT methylation status. Increased expression of GPNMB, CCL5 and KLRC1 (associated with immune suppression, invasion and aggression) and polarisation towards an M2 phenotype (increased CD163 and MSR1 expression) in post-treatment tumours demonstrated an overall change in the tumour microenvironment favouring aggressive tumour growth and disease progression.

Conclusion: These findings highlight the ability of glioblastomas to evade not only the toxic onslaught of therapy but also to evade the immune system suggesting that immune-altering therapies may be of value in treating this terrible disease.

Killing glioma cells by activating the cAMP pathway via phosphodiesterase (PDE) inhibition: Can PDE inhibitors be repurposed for the treatment of high-grade glioma?

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Abstract

Aims: To determine how activation of cAMP, using phosphodiesterase inhibitors (PDEi), kills glioma cells and inhibits brain tumour growth.

Methods: We used a panel of six human glioblastoma (GBM) cell lines to investigate the mechanisms by which cAMP signaling triggers apoptosis[1]. Western blotting and cell viability assays were used to test the effects of single agent and combinations of cAMP agonist forskolin, and PDEi IBMX, in combination with temozolomide (TMZ) and a MAPK small molecule inhibitor.

Results: In three out of six cell lines, activation of cAMP signaling alone led to increased apoptotic cell death, as evidenced by increased expression of Annexin-V and pro-apoptotic protein, Bim. The other three GBM cell lines were less sensitive to forskolin and/or IBMX. These cell lines exhibited high MAPK activity, in contrast to the more sensitive cells which demonstrated relatively low MAPK activity, therefore endogenous MAPK appears to regulate sensitivity to cAMP activation induced cell death. This was confirmed by combining forskolin-IBMX with the MAPK inhibitor, U0126 with the combination treatment resulting in efficient GBM cell death in the cells with lower sensitivity to forskolin-IBMX alone. In all cell lines, addition of TMZ enhanced apoptosis. In preliminary in vivo experiments, we tested the effect of cAMP activating drugs in an in vivo brain cancer model we developed and show that forskolin-IBMX administration delays tumour growth.

Conclusions: Our data offers a new rationale for GBM treatment using standard chemotherapeutic compounds in combination with PDEi, including FDA-approved anxiolytic drugs such as ampremilast, which have the added advantage of proven blood-brain barrier crossing.

1. Daniel P et al., Cell Death & Disease, 7(12): e2494.
2. Daniel P et al., bioRxiv, doi.org/10.1101/143388.

Isolation and Analysis of Brain Cancer Patient Circulating Tumour Cells and Circulating Tumour DNA

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Abstract

Background

The poor prognosis of brain cancer is partly due its aggressiveness, but also to the difficulty in achieving good surgical margins. In some patients, access for biopsies is difficult or impossible. Three years ago, circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) were discovered in the blood of brain cancer patients. This project examines the potential of a 'liquid biopsy' in monitoring the outcome of brain cancer patients.

Methods

A combination of antibodies suitable for GBM-CTC isolation was determined using flow cytometry and immunocytostaining. The suitability of these antibodies for immunomagnetic CTC isolation was confirmed in GBM patient blood samples (n=12). Single CTCs were isolated and whole genome amplification (WGA) performed. CTC DNA was then analysed for a known prognostic GBM biomarker, the IDH1 mutation R132H, with a droplet digital PCR (ddPCR) assay we developed. Plasma was isolated from the same patients to extract ctDNA, to be used to detect methylation of O6-methylguanine DNA-methyltransferase (MGMT) based on a novel methylation-sensitive digestion ddPCR assay. The MGMT assay is currently being tested in our patient cohort.

Results

GBM CTCs were successfully isolated and identified using a combination of brain-cancer specific antibodies. Approximately 70% of patients were found to have GBM CTCs (n=8/12). From optimisation, it has been determined that IDH1-R132H mutant testing is successful from as few as 5 CTCs in a background of lymphocytes without WGA, and in single cells after WGA. Patient CTCs are currently being tested for IDH1 mutation. The MGMT methylation assay can detect two DNA molecules that have been methylated in a background of 2000 non-methylated ones.

Conclusions

The results of this project suggest that liquid biopsies in GBM have clinical potential to detect genomic and epigenomic changes from the circulating tumour material.

Understanding mechanisms of IDH-mutant glioma progression and recurrence through use of latest-generation mass spectrometry

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Abstract

Background/Aims: Gliomas are the most common primary brain tumours in adults. IDH-mutated low grade gliomas have a relatively indolent clinical course; however, over time they progress to a higher grade. Initial standard of care involves surgery with the addition of radiation and alkylating chemotherapy for more aggressive lesions. Molecular studies revealed recurrent tumours harboured more mutations upon malignant progression when treated with chemotherapy and/or radiotherapy compared to treatment-naïve tumours. To ascertain the natural history and treatment-induced effects of progressive IDH-mutated 1p19q intact tumours, this study compared differences in the proteomic profiles of 6 matched pairs of primary lesions with their higher-grade recurrent lesion.

Methods: Tumour specimens from three patients who presented with grade 2 lesions and following resection were collected. Time to recurrence (TTR) for these patients was 38, 30 and 14 months respectively. Tumour from another three patients who presented with grade 3 lesions and received radiotherapy alone following surgery were also analysed. Their TTR was 99, 52 and 71 months. Protein was extracted from frozen specimens and following quality control analysed by SWATH-MS (on a Sciex TripleToF 6600).

Results: Overall, 1781 proteins were identified by SWATH-MS analysis. Of those proteins, 32 were significantly differentially expressed (FC ≥2-fold; $p \leq 0.05$) between primary and recurrent specimens. In both datasets, these key proteins were associated with activation of the Acute Phase Response, Cell Death and Survival and Cellular Compromise, Development and Movement. Proteins significantly differentially expressed included LG3BP, VTNC, KAP0 and FUMH which are involved in tumour formation and progression and altered cellular metabolism.

Conclusions: The identification of differentially expressed proteins will improve our understanding of the mechanisms driving recurrence and progression of gliomas and may also reveal potential novel targets for additional therapies for this deadly cancer.

A collection of primary cell line and xenograft models of proneural, classical and mesenchymal glioblastoma

Brett Stringer[1], Bryan Day[1], Paul Jamieson[1], Kathleen Ensbey[1], Zara Bruce[1], Yi Chieh Lim[1], Kate Goasdoué[1], Suzanne Allan[1,2], Thomas Robertson[2], Peter Lucas[2], Gert Tollesson[2], Scott Campbell[2], Craig Winter[2], Hongdo Do[3], Alexander Dobrovic[3], Po Inglis[2], Rosalind Jeffree[2], Andrew Boyd[1,4]

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Abstract

Background: Many preclinical and laboratory investigations of human GBM use cell lines. Low passage, primary (patient tissue-derived) cell lines that recapitulate the cardinal features of GBM are a gold standard, however many investigators baulk at using them for reasons that include the difficulty in accessing patient tissue to establish such lines and the lack of phenotypic information often associated with acquiring them elsewhere.

Aim: To facilitate their more widespread use, we sought to establish a set of tractable tumourigenic primary GBM cell lines representing different molecular subtypes of GBM with detailed genotype and phenotype information.

Methods: Tumour tissue was collected following informed patient consent and with human research ethics committee approval. Primary cell lines were established in serum-free medium supplemented with EGF and FGF2 on matrigel. Mycoplasma testing, STR profiling, exome sequencing, RNA microarray analysis, flow cytometry, MGMT pyrosequencing, cell proliferation measurement, antibiotic sensitivity determination and xenograft testing in NOD/SCID mice were performed.

Results: Patient (age, sex, survival), pathology (report and histology), and detailed cell line (morphology, proliferation rate, exome sequence, IDH1 status, STR profile, MGMT methylation status, gene expression, molecular subtype, antibiotic sensitivity) and xenograft model (histology and median survival) data have been established. A set of lentiviral vectors also has been developed and deposited with Addgene for making the cell lines bioluminescent and for targeted gene investigation by over-expression or CRISPR/Cas9 inactivation. The cell lines are freely-available for research purposes and all data can be accessed from a single website (Q-Cell).

Conclusion: These resources should prove valuable to researchers looking for readily-accessible, clinically-relevant, well-characterised models of GBM, especially those without ready access to patient tissue.

Targeting the Pentose Phosphate Pathway as a Treatment For Paediatric Brain Rhabdoid Tumours

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Abstract

Introduction: Atypical teratoid rhabdoid tumors (ATRT) are rare, highly aggressive paediatric brain malignancies with a 5-year survival rate of 67%. Current treatments are largely ineffective, leading to very poor prognosis and a cancer relapse time of around 11–20 months. Recent discoveries on cell metabolism have revealed the significance of metabolic mechanisms for cancer growth and targeting these pathways have detrimental effects on cancer survival. The metabolic pathways of brain AT/RT remains to be explored.

Methods: ATRT cell lines (BT-12 and CHLA-266), Malignant Rhabdoid Tumour cells (G401) and normal human kidney cells (HEK293T) were investigated. Metabolic activity, such as oxidative phosphorylation and glycolytic activity was examined using the Seahorse XF analyser. Expression of metabolic genes were analysed using Qiagen PCR arrays and confirmed with RT-PCR.

Results: Metabolic analysis revealed ATRT and MRT cells had significantly high glycolysis and reduced oxidation as compared to HEK293T cells. Microarray PCR of metabolic genes revealed enhanced glycolytic expression in RT cells as compared to HEK293T and interestingly, the pentose phosphate pathway (PPP) genes were significantly upregulated. Inhibition of the PPP pathways with 6-aminonicotinamide (6AN), significantly reduced cell growth of AT/RT by 59.3%$\pm$5.5 and MRT cells by 35.02%$\pm$2.3, however no toxic effect was observed with the normal cells.

Conclusion: AT/RT and MRT cells showed upregulation of glycolytic pathways, in particularly the pentose phosphate pathway. Inhibition of the PPP pathways significantly inhibited cancer growth and showed no effect on normal cells. Targeting this pathway reveals an alternative therapeutic for this highly aggressive childhood cancer.

DELEGATES LIST

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A/Prof Maciej Mrugala	Mayo Clinic
Dr Melinda Munns	Bristol-Myers Squibb
Dr Vanaja Muthurajah	WellingtonSCL
Dr Najmun Nahar	CPMCC, Westmead Hospital
Dr Nichola Naidoo	Wellington Hospital
Mr Stephen Newman	Brain Tumour Alliance Australia
Prof Anna Nowak	University of Western Australia
Dr Chelsie O'connor	Genesis
Prof John Olver	Epworth Hospital
A/Prof Geraldine O'Neill	The Children's Hospital at Westmead
Mr Martijn Oostendorp	NHMRC-Clinical Trials Centre
Dr Jonathon Parkinson	Royal North Shore Hospital

Mr Dustin Perry	Cure Brain Cancer Foundation
Mrs Jennifer Philip	Department of Medicine, University of Melbourne, St Vincent's Hospital and VCCC
Dr Claire Phillips	Peter MacCallum Cancer Centre
Ms Susan Pitt	Brain Tumour Alliance Australia Inc
Ms Cheree Porter	Olivia Newton John Cancer and Wellness Centre
Ms Victoria Prior	Kids Research Institute
Dr Andrew Pullar	Princess Alexandra Hospital
Dr Leonie Quinn	Department of Cancer Biology and Therapeutics, John Curtin School, The Australian National University,
Dr Thulasi Rajah	Royal Brisbane Hospital
Ms Emma Reiterer	Cabrini
Dr Angela Rezo	The Canberra Hospital
Mrs Julia Robertson	Brain Tumour Alliance Australia
Dr Michael Rodriguez	Neuropathology Consulting Services
Prof Stephen Rose	CSIRO
Prof Mark Rosenthal	COGNO
Ms Rigoula Roussakis	Brain Tumour Alliance Australia
Mr Michael Ruemelin	Brainlab
Dr Mythily Sachchithananthan	BCBA
Dr Rasika Samarasinghe	Deakin University
Ms Carolina Sandler	Queensland University of Technology/University of Queensland
Ms Kirsten Seletto	Cabrini
Dr Sarah Shigdar	Deakin University
Dr Brindha Shivalingam	Chris O'Brien Lifehouse
Miss Michelle Simango	Deakin University
Prof John Simes	NHMRC-Clinical Trials Centre
Mr Philip Steel	Brain Tumour Alliance Australia
Ms Michelle Stewart	Cure Brain Cancer Foundation
Dr Brett Stringer	QIMR Berghofer Medical Research Institute
Dr Lisa Sullivan	The Canberra Hospital
Dr Achiraya Teyateeti	Faculty of Medicine Siriraj Hospital, Mahidol University
Dr Rowena Thomson	Brainlab
Mr Robert Tobler	Peter MacCallum Cancer Centre
Dr Gurvinder Toor	Royal Melbourne Hospital
Mr Luke Unicomb	AbbVie
Ms Vanessa van den Berg	Specialised Therapeutics
Prof David Walker	NEWRO Foundation
Mr Gerry Ward	Cabrini
Dr Patrick Wen	Dana-Farber Cancer Institute
Dr Helen Wheeler	NSCC
Dr James Whittle	VCCC / WEHI
Mrs Celia Williams	Robert Connor Dawes Foundation
A/Prof Lee Wong	Biomedicine Discovery Institute, Monash University
Dr Jin-san Yoo	PharmAbcine, Inc
Dr Tanya Yuen	Royal Melbourne Hospital

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