Making Education Easy 25-26 October 2013, Sydney

In this review:

Welcome to this review of the 6th Cooperative Trials Group for Neuro-Oncology (COGNO) Annual Scientific Meeting (ASM).

COGNO continues to grow both in membership and stature, with a record number of attendees and submitted abstracts for the 2013 ASM. COGNO held its 6th ASM from October 25th - 26th, its first inaugural 'stand-alone' ASM. COGNO was pleased to host four internationally renowned guest speakers:

Professor Mitchel Berger, Neurosurgeon from the University of San Francisco, USA

Professor Jan Buckner, Neuro-oncologist from the Mayo Clinic Cancer Center, USA

Professor Peter C. Burger, Neuropathologist from the Johns Hopkins Hospital, USA

Associate Professor James R. Perry, Neuro-oncologist from the Sunnybrook Health Science Centre, Canada

One of the major themes of the 2013 COGNO ASM was 'Challenges of Neuro-oncology in the Younger Adult'.

Inter-disciplinary presentations from international and national experts spanned the advances in the understanding and molecular pathogenesis of low grade glioma, the evidence supporting modern neurosurgical techniques which maximise resectability whilst minimising morbidity in low grade glioma, updates on seizure management – a common clinical issue in low grade glioma, as well as supportive care/coordination for this patient and carer group with complex needs. There were excellent overviews of the current state of evidence and controversies regarding treatment options, especially the role of chemotherapy for grade II and III astrocytoma and oligodendroglioma, and in particular, the need for stratification by biologic prognostic factors including 1p19q LOH status, IDH1 mutation and MGMT methylation status.

Selected talks also addressed the current issues facing the adolescent and young adult (AYA) neuro-oncology population, including advances in molecular pathogenesis, stratification and treatment strategies for tumours such as medulloblastoma. In addition, there was a session dedicated to discussing the role of angiogenesis inhibitors (in particular bevacizumab) in neuro-oncology, and an update on both phase III NCIC-EORTC-TROG trials in low grade glioma and the elderly with glioblastoma.

Video presentations of selected speakers will be made available via the COGNO website in due course.

I hope you find this conference review useful and look forward to your feedback.

Kind Regards,

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Further information regarding COGNO can be found at http://www.cogno.org.au/

Improved responsiveness to Temozolomide by blocking MIF expression in glioblastoma

Presenters: McDonald KI et al.

Summary: In this study the low molecular weight proteome was assessed in 48 uniformly-treated patients with glioblastoma (GBM) using Surface Enhanced Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (SELDI-TOF-MS) in order to identify aberrant protein expression associated with resistance to chemoradiotherapy. Patients with treatment-refractory tumours and with poor overall survival showed a high expression of macrophage inhibitory factor (MIF), a pro-inflammatory cytokine/chemokine which contributes to tumorigenesis. A total of 69% (n=230) of all GBM showed high MIF protein expression and this was associated with poor prognosis. Inhibiting cellular MIF with siRNA or adding an inhibitor of the tautomerase activity site of MIF to RN1 cells both increased the efficacy of Temozolomide (TMZ). Although methylation of the MGMT promoter region of the tumour is a strong predictor of whether chemoradiotherapy will be beneficial, MIF signalling may also contribute to TMZ resistance.

Comment: Chemoradiation resistance remains a paramount ongoing challenge in the management of GBM. Building on current evidence that MGMT methylation status is both an important (favourable) prognostic and predictive factor, McDonald *et al* report that high expression of the inflammatory-related protein MIF was associated with a poorer prognosis, and moreover, that the binding of MIF to its receptor complex, CD74/CD44, promotes chemoradiation resistance. Sensitivity to TMZ was significantly improved when the MIF inhibitor ibudilast was added. A combination of TMZ plus ibudilast will be further investigated as a novel treatment for patients with MGMT non-methylated tumours as well as recurrent tumours.

Microparticle-derived small RNAs in glioblastoma

Presenters: Buckland ME et al.

Summary: This *in vitro* study aimed to characterise the small noncoding RNAs (sncRNA) population in microparticles (MPs) obtained from GBM cells and assessed the response of brain endothelial cells when exposed to these MPs. MPs were harvested from U251 GBM cells following which MPs and their contents were characterised using various analytical techniques. Pre-defined quantities of MPs were added to primary human brain endothelial cells and expression microarray profiling was then conducted. The results showed that abundant and selectively packaged RNA species were present in GBM MPs. Although, in general, microRNAs (miRNAs) were depleted, miRNAs involved in cancer were enriched. MPS were also enriched for RNAs involved in drug resistance and for intergenic sncRNAs. A variety of gene expression changes in microvascular endothelial cells also occurred in response to glioma MPs. This study shows that MPs play a major role in the signalling pathway in glioblastomas.

Comment: This study investigated a potential signalling pathway in GBM MP-derived sncRNAs. MPs are a newly recognised form of intercellular communication. Buckland *et al* hypothesised that intercellular transfer of sncRNAs via glioma MPs could represent a mechanism whereby a tumour can modify its environment to permit tumour growth and invasion. The use of sncRNAs deep sequencing demonstrated that many sncRNAs are selectively packaged into MPs, many of which had unknown function. Further characterization of MP content of GBM stem cells may have broader implications for future novel diagnostic and therapeutic strategies.

EphA3 maintains tumorigenicity and is a therapeutic target in glioblastoma multiforme

Presenters: Day BW et al.

Summary: Eph receptor expression was analysed in 80 glioma specimens and EphA3 expression with known glioma tumourigenic markers was analysed in 9 dissociated specimens in this study aiming to identify EphA3 as a functional, therapeutically targetable protein in GBM. The tumorigenic potential of EphA3 was assessed by down regulating EphA3 using short hairpin RNA (shRNA) depletion, and tumour formation was assessed using *in vivo* bioluminescence. A lutetium-radiolabelled EphA3-specific monoclonal antibody (mAb) was used to assess EphA3 *in vivo* targeting. The results showed that over expression of EphA3 is common in GBM, particularly in the mesenchymal subtype. The tumour-initiating cell population in glioma showed high expression of EphA3, and EphA3 plays a critical role in maintaining tumour cells in an undifferentiated state by modulating MAPK signalling. The tumorigenic potential of EphA3 was greatly reduced by EphA3 knock down or depletion of EphA3-positive tumour cells. EphA3 may be a relatively tumour-specific therapeutic target in GBM.

Comment: This study highlights the possible role of the receptor tyrosine kinase EphA3, as a functional, targetable protein in GBM. Day *et al* report that EphA3 was frequently over-expressed in GBM, especially in the aggressive mesenchymal subtype. EphA3 was highly expressed in the tumour-initiating cell population in glioma which is thought to be key in maintaining tumour cells in an undifferentiated state. Moreover, these mechanisms may be responsible for tumour recurrence following treatment.

An audit of the quality of pathology reporting in high grade glioma (HGG)

Presenters: White A et al.

Summary: The histopathology reporting quality in grade III/IV gliomas was assessed for 28 elements of the Central Nervous System Tumours Structured Reporting Protocol. Nine parameters were assessed to provide a summary quality score: use of WHO criteria; description of cell type; grading of tumour; narrative supporting cell type and grade; absence of equivocal language; conclusion reporting cell type and grade; conclusion aligned with report narrative. Of 594 pathology reports, the conclusion, tumour classification and tumour grade were not supported by the report narrative in 21%, 18% and 6% of reports, respectively. All 9 quality score-related criteria were fulfilled by only 24% of reports. Quality scores were significantly higher for reports by neuropathologists than general pathologists (7.67 vs 6.62), reports of grade III versus grade IV tumours (7.77 vs 7.06) and reports of initial resections or resections of transformed low grade tumours versus resections of recurrent tumours (7.5 vs 7.53 vs 6.1).

Comment: The study by White *et al* highlighted that even in the context of patients recruited to a glioma epidemiology study, there were a range of deficiencies in pathology reporting, with specific report content and conclusions not always supported by the narrative, and with only 5% using a synoptic template. Quality scores were higher for initial versus recurrent resections, and specialist versus general pathologists. High quality of glioma pathology reporting is integral to clinical management and accurate prognostication. Improved uptake and application of the RCPA CNS Tumours Structured Reporting Protocol, released in 2011, may aid in achieving these outcomes (http://www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols).

Patients aged 65-75 with glioblastoma may still benefit from long course radiotherapy with Temozolomide

Presenters: Gzell CE et al.

Summary: This study investigated the outcome of 109 elderly patients with grade IV GBM managed with hypofractionated (40Gy) or long course (60Gy) radiation therapy (RT). Baseline ECOG performance status, RT dose and TMZ use was recorded, and overall survival was calculated from date of diagnosis. Results showed that overall median survival (MS) was 12 months (95% CI 11-13) with 12% of patients surviving longer than 2 years. Near total resection (p=0.036) was associated with improved MS but ECOG grade 0-1 was not (p=0.34). Of patients aged 65-75 years, 55% were managed with 40Gy, 45% with 60Gy and 70% with TMZ. TMZ (13 vs 8 months; p<0.0001) and 60Gy (15 vs 9 months; p<0.0001) use was associated with longer survival. MS was longer with 60Gy than with 40Gy (15 vs 11 months; 95% CI 13-17 vs 9-13 months) in the 70% of TMZ-treated patients. ECOG grade 0-1 was not associated with improved survival.

Comment: The optimal management of the elderly patient with GBM remains controversial, with the aim of maximising treatment efficacy and QOL whilst minimising treatment-related toxicities in this group with overall poorer outcomes. Compared to the gold standard Stupp *et al* EORTC regimen using radiation (60Gy over 6 weeks) with concurrent TMZ followed by 6 months of adjuvant TMZ, two phase III RCTs published in 2012, the NOA-08 study by Wick *et al* and the Nordic study by Malmström *et al*, utilised differing dose schedules of radiation and chemotherapy but comparative results were not able to articulate an optimal treatment algorithm. A third phase III NCIC-EORTC-TROG RCT (ClinicalTrials.gov identifier: NCT00482677) recently closed to recruitment (n=562 patients) in September 2013. This trial defined elderly as ≥ 65 years, and randomised patients to hypofractionated radiation (40Gy over 3 weeks) versus the 40Gy schedule with concurrent and adjuvant TMZ for up to 12 months. Companion molecular studies, including MGMT methylation status, were also undertaken. It is hoped that the results of the NCIC study will help clarify a superior treatment strategy for elderly patients with GBM.

Comparative longitudinal assessment of psychosocial distress between malignant and benign primary brain tumours in a patient-carer cohort

Presenters: Trad W et al.

Summary: This study compared psychosocial distress (PSD) levels between patients with malignant or benign primary brain tumours (PBT), and in their carers. PSD was measured in PBT patients (n=110) and carers (n=36) using the NCCN Distress Thermometer (DT) [score: 0=none, 10=extreme] at initial diagnosis and at first recurrence. The DT scores were 4 at diagnosis and 7 at recurrence, in high grade GBM patients (n=38) and 3 at diagnosis and 6 at recurrence in benign brain tumour (BBT) patients (n=52). Both groups had equivalent numbers of patients with a DT score >4 and average scores were 6 at diagnosis and 8 at recurrence. Carer DT scores were higher than patient scores at diagnosis (5 vs 3) and at recurrence (8 vs 6) across both GBM and BBT groups. The study shows that PSD is high in patients with malignant and benign PBT, and carer distress is higher than that of patients.

Comment: The study by Trad *et al* highlights firstly, the need to undertake systematic psychosocial assessment and timely care coordination to both screen for and address complex care needs in PBT patients. Secondly, the finding that psychosocial distress of carers was higher than patients both at tumour diagnosis and also at recurrence is important, emphasizing that carers warrant specific screening and support. Furthermore, BBT patients with elevated longitudinal distress over an often extended survivorship trajectory is also an under-recognised issue that deserves greater clinical attention by neuro-oncology services.

Phase 1 trial of adoptive cytomegalovirus-specific T cell therapy for recurrent glioblastoma: results and future prospects

Presenters: Walker D et al

Summary: This phase 1 study investigated autologous cytomegalovirus (CMV)-specific T cell therapy used in combination with chemotherapy for recurrent GBM. Of the 21 enrolled patients with recurrent GBM, eleven had received up to four treatments and autologous CMV-specific T cell. Standard treatments, including TMZ, were continued by all patients. The CMV-specific T cells targeted MHC class I- and class II-restricted epitopes. The results showed that combination therapy was well tolerated with only minor adverse events observed. Overall survival since first recurrence ranged from 174 to 2352 days. Median overall survival was 580 days which was greater than the median overall survival in patients not receiving T cell therapy (110 days). CMV-specific T cells from patients receiving T cell therapy displayed distinct gene expression signatures which correlated to clinical response.

Comment: Walker *et al* presented the results of a novel phase I study in recurrent GBM patients based on autologous CMV-specific T cells used in combination with other therapies. Notably, CMV-specific T cells from these patients displayed distinct gene expression signatures which correlated with clinical response, a few of which were quite striking. Whilst feasibility and safety of this novel therapy was demonstrated, the role and incorporation of immunotherapy such as T-cell therapy in clinical practice has yet to be clarified. Further research from this collaborative group will apply this treatment strategy to newly diagnosed GBM patients in 2014.

Distance of melanoma metastasis to the hippocampus: estimated safety of hippocampal-sparing whole brain radiation therapy

Presenters: Hong A et al.

Summary: This study aimed to report the prevalence of melanoma metastasis within the hippocampus and to identify variables correlating with the presence of hippocampal metastases. Pre-local treatment MRI scans from 77 patients enrolled in the phase 3 ANZMTG 01.07 WBRTMel trial were assessed to determine the volume, location and closest distance of each metastasis to the hippocampus, and the influence of factors on the location of a metastasis within 5mm of the hippocampus. Of the 115 metastasis, none were in the hippocampus. The distribution of metastasis was frontal (53.5%), parietal (20%), temporal (11.3%), occipital (15.7%), cerebellum (67%) and pineal gland (0.87%). The metastases was within 5mm of the hippocampus in 5.2% of patients (n=4), and the median distance between the metastasis and hippocampus was 37.2mm. The only significant predictor for the risk of a hippocampal metastasis was the total volume of metastases (OR 1.071; 95% CI 1.003 –1.144; p = 0.04).

Comment: The rationale for hippocampal-sparing radiation is to avoid adverse effects on the neurogenic stem cells thought necessary for neurogenesis, thereby potentially avoiding longer-term neurocognitive sequelae of radiation, yet without compromising intra-cerebral control of disease. The results of Hong *et al* confirm the results of previous phase II studies supporting a low incidence of metastases residing either in or within close proximity to (within 5mm) the hippocampus. These findings in the setting of melanoma metastases suggest that hippocampal-sparing whole brain radiation therapy (HS WBRT) does not compromise treatment efficacy. Several phase III randomised, controlled trials in other clinical settings e.g. small cell lung cancer and prophylactic cranial irradiation (with or without HS WBRT) are addressing this topic.

6th COGNO Conference Review™

Selection and review of the research carried out by Dr Eng-Siew Koh, a staff specialist in radiation oncology at Liverpool Hospital, NSW, and is also the current chair of the Clinical Oncological Society of Australia (COSA) Neuro-oncology Group. She was the convenor for the 6th COGNO ASM.