

British Neuro Oncology Society (BNOS) Conference Report 2017

Approximately 250 people with an interest in neuro-oncology attended part or all of “Engaging Science, Enhancing Survival” in Edinburgh from 21 – 23 June 2017. In addition to our guest speakers, including a number from North America, Denmark and Italy, and wide representation from throughout the UK, there were also proffered papers from Greece, Hong Kong, and India.

As well as the plenary sessions, including the Clerk Maxwell Cancer Lecture and the Stephen Baker Memorial Lecture, there were proffered papers, posters, and lunchtime seminars and exhibitions by sponsors. There were often parallel sessions so that attendees could choose between science, clinical and allied patient care topics such as Quality of Life and Palliative Care. Bursaries were available to ensure that those starting out in the field could attend. Of course the social and networking opportunities were not ignored with a Welcome Reception at Dynamic Earth and the Conference Dinner taking place at the Playfair Library.

BNOS would like to thank the various organisations and charities whose sponsorship made this meeting possible: AbbVie, BrainLab, Medac, Braintrust, Brain Tumour Research, B Braun, Bristol-Myers Squibb, Cancer Research UK, Codman, Integra, International Brain Tumour Alliance, Medtronic, Mercian, Novartis, Renishaw, Severn, Storz, The Brain Tumour Charity, TrusteDoctor, Vitaflo.

Council would also like to acknowledge the hard work of the Edinburgh team led by Imran Liaquat. Sessions were filmed, and will be made available on the BNOS website, and the abstracts of the proffered papers and posters are available to all via the conference website. This report is intended to provide a flavour of the Conference via some of the themes that stood out amongst the sessions that I attended.

Glioma Stem Cells

Glioma stem cells underpin malignancy and recurrence via their angiogenic and invasive nature and resistance to chemo-radiation. The vascular microenvironments of neural and glioma stem cells differ, with two types of signalling, maintaining quiescence amongst the former and the perivascular invasion characteristics of the latter. New insights into the genomic and epigenomic landscape of glioma were discussed frequently. Whilst the former, of course, continues to be studied e.g. helping understanding of how IDH mutation confers better prognosis via a significant enrichment of genes involved in apoptosis and endoplasmic reticulum stress response, inhibitors of epigenetic regulatory proteins are now also a focus. Hence, there were papers describing development of animal models to replicate both aspects and not just single nucleotide variations. Insights into neuronal differentiation as a potential therapeutic avenue for GBM were also presented. Preclinical data was presented demonstrating that a subset of Ascl1-expressing patient-derived glioma stem cell lines can be induced to differentiate into neurons, leading to pronounced tumour suppression and extended survival.

The FOXG1 and SOX2 transcriptional factors found in high levels in glioma drive unconstrained self renewal of neural stem cells. This is effected by preventing premature differentiation via control of the core cell cycle apparatus and epigenetic machinery. As SOX2 and OLIG2 progenitors are absent in adult brain, but cycling rapidly in the foetal brain, work is now progressing to investigate whether the Zika virus (which is known to result in congenital birth defects whilst having little effect when non-pregnant adults are infected) penetrates and targets glioma stem cells.

Early Diagnosis

It can be argued that there is no advantage to be gained from earlier diagnosis of adult brain tumours as there is no evidence that this would positively affect outcome, but just increases the period of anxiety for patients and their families. However, the contrary view was made strongly that a long symptomatic period prior to diagnosis (particularly in those with more subtle symptoms than seizures) leads to poor quality of life, frustration and psychological damage. Early diagnosis therefore should be a priority and a better triage procedure is required to help GPs know whom to refer for urgent imaging. Analysis of open-access Computed-Tomography referrals for possible CNS malignancy by Lothian-based GPs for 2010-2015 showed a rate of only 1.6% of scans positive for brain tumour, headache (either alone or in combination with other symptoms) being the commonest complaint amongst patients with positive scans.

A potential infrared spectroscopic method based on a serum sample is being developed as a cancer/no cancer test (95% sensitivity and 88% specificity). It takes 10 minutes and could be utilised in a GP practice. This was thought to be economically viable, the incremental cost-effectiveness ratio per quality-adjusted life year (QALY) being far below the NICE threshold of £20,000 - £30,000 (although the cost of additional secondary care if a case was diagnosed earlier was not included). However, there are also other factors to be considered e.g. would a GP feel able to withhold referral after a negative test even though symptoms had justified invoking the test in the first place?

Biomarkers

It was encouraging to hear that the WHO 2016 biomarker-based classifications appear to be well established. Indeed it was suggested that the next classification will be significantly different again and that the review time span of nine years may be too long. In particular, IDH wild-type astrocytoma is considered only a provisional entity within the new classification as these can have very variable prognosis. There is a growing view that they can be further classified into molecularly high grade (harbouring EGFR, H3F3A or TERTp mutations) and lower grade. The former are a distinct, rapidly progressive subgroup without histopathological Grade 4 characteristics but suspected to represent early glioblastomas (“baby GBMs”) whereas the latter lack all of these biomarkers, the most favourable survival being noted in those with MYB amplification.

It was thought that adult glioma patients should be informed as to their IDH mutation and MGMT promoter status, and the implications, as they have such a dramatic effect on treatment response and outcomes.

The role of biomarkers in the sub-classification of medulloblastoma (first to four and now to seven or possibly 12 sub-groups) is now evident in impact on treatment, most notably the possibility of reducing aggressive treatment in the better prognosis sub-groups so as to limit the significant long term toxicity.

Imaging

One might be forgiven for thinking that biomarker assays could now drive all diagnosis and treatment decision-making; however, tumours are notoriously heterogeneous and plastic over time and it is not always possible to obtain the repeated tissue samples required to conduct assays. Hence, while identification of biomarkers is now vital, there is definitely still a role for (ever more) sophisticated imaging techniques and integrated diagnostic-phenotypic-genotypic methods. For example, magnetic resonance perfusion imaging may replace conventional MRI techniques that fail to detect the regions of low tumour cell density remaining after resection but which are responsible for subsequent tumour recurrence, diffusion-weighted MRI may identify non-enhancing IDH wildtype tumours despite an initially innocuous imaging appearance, and PET/CT can differentiate tumour phenotypes and between disease progression and radio-necrosis.

Despite the significant engineering challenge, a multi-modality imaging tool for concurrent spectroscopy and MRI has been built via the EU-funded INSERT (INtegrated SPECT/MRI for Enhanced stratification in Radio-chemo Therapy) project. A prototype is now available, providing simultaneous biological readouts aligned with high quality anatomical information, which should enhance stratification and early treatment response assessment without the confounding problem of pseudo-progression seen when MRI alone is utilised.

Surgery

Formal surgical trials are rare. For example, although a systematic review of studies investigating efficacy and safety of 5-ALA-guided resection has identified 46, they are mostly only deemed Level 2-3 evidence. Although use of 5-ALA correctly identifies tumour tissue, there are sensitivity and specificity limitations. Hence, it was encouraging to hear of proposals for two prospective multi-centre trials to compare intra-operative imaging techniques (MRI and ultrasound) and 5-ALA with white light microscopy.

The Bristol team reported, however, that although awake surgery and intra-operative MRI are the most effective individual aids in preventing damage to functional brain while maximizing the extent of resection, and despite high levels of patient satisfaction, using them together is demanding for the anaesthetic and nursing teams and for the patient, at 10 hours the



theatre times being about two hours longer than for a standard craniotomy. Hence the combination is mostly only used for Grade 2 tumour resections and those Grade 3-4 tumours possibly implicating eloquent areas.

It was depressing to hear of the very slow uptake of use of 5-ALA across the UK; an audit of neuro-surgical centres and their catchment areas shows that even though only one unit has no interest in using it, and all others have surgeons trained in its use, only 43% of centres have fully implemented its use, with a further 23% using it to a limited extent. The only two (foreign) studies which calculated cost effectiveness provide a cost per QALY of £6500-7400 (although only one takes into consideration all medical costs) but even so the barrier remains one of funding. As all efforts to obtain full NHS approval for its use have failed (and the recent approval of 5-ALA in the USA is not expected to have any significant impact on UK usage), surgeons should perhaps be creative in finding savings elsewhere in order to fund its use? For example, in Southampton measures have been introduced to ensure high rates of elective admissions and reduced length of stay (LOS). Their median LOS for intrinsic tumours is 1 day (versus 6 days nationally). Mean LOS (vs national) is 2.5 (6.4) days for high grade glioma, 2.9 (6.5) days for metastases and 4.7 (9.2) days for benign tumours - all the lowest in the UK - without compromising readmission, re-operation or mortality rates. [The use of the National Neurosurgical Audit Program (NNAP) and Get It Right First Time (GIRFT) data for benchmarking was recommended.] Not only has this proven popular with patients, but it has improved efficiency, reduced cost, cancellations and waiting times and has more widespread implications across the NHS.

Local Drug Delivery

We know that residual cancer cells remain at the margin even after gross total resection and that targeting this invasive region is vital in the development of new therapies. Hence there is significant interest in locally delivered chemotherapy.

The Nottingham team is delivering combined temozolomide and etoposide directly into the resection cavity in a thermo-setting biodegradable paste and this has achieved significant extension to overall survival in an orthotopic rat model. Similarly encapsulated disulfiram nanoparticles have been developed in Wolverhampton to protect the drug from degradation, thereby extending its half-life, and this in combination with copper significantly inhibits glioma in orthotopic xenograft mouse models at a very low dose.

In Bristol convection-enhanced delivery of panobinostat-loaded nano-micelles allows administration of the water insoluble HDAC inhibitor in a high-grade glioma rat model. An added sophistication being studied in Edinburgh is that of coupling a prodrug with the use of a non-toxic and catalytic implant to trigger local release of cytotoxic agents. The prodrug is initially rendered non-toxic by masking the functional-groups key to its mode of action, then unmasked by palladium in the implant. As the palladium device catalytically unmasks the prodrug, the treatment course would not be limited by the lifetime of the implant and could be readily repeated in cases of recurrence.

An example of local delivery which has reached man is that of irinotecan incorporated into biodegradable hydrogel microspheres for injection into the post-surgical cavity wall. A Phase I study in Birmingham has shown less local swelling and wound healing issues than have been demonstrated for carmustine wafers despite early offloading. However this shorter period of exposure is compensated for by a much higher than expected activation of irinotecan to its active metabolite.

Radiation Therapy

Even with stereotactic radiosurgery alone (without whole brain irradiation) recent studies have demonstrated that around half of patients suffer memory impairment. Hence, having identified that a considerable proportion of patients receiving radiosurgery for isolated metastases receive significant radiation to the hippocampus, a proposed new prospective study in Wales will correlate detailed radiation dosimetry, neurocognitive function and functional MRI measurements of organs at risk.

It was interesting to hear that TTFIELD treatment is now being considered in the UK. In Nottingham an early study has shown anti-proliferative effects on paediatric brain tumour cell lines at clinically deliverable field settings and implantable multiple deep brain stimulation electrodes may address the compliance issues associated with the Optune system.



There is also a focus on identifying novel therapeutics to overcome inherent radioresistance. Irradiation of glioblastoma cells can, for example, promote enhanced motility and invasiveness, both in vitro and in vivo, through activation of myotonic dystrophy kinase-related CDC42-binding kinase, thought to offer a potential new target. Radio-sensitisation can also be engendered in glioma stem cells by poly ADP ribose polymerase (PARP) inhibitors, the most developed being olaparib, which is being studied in the PARADIGM clinical trials, and an ataxia–telangiectasia mutated kinase (ATM) inhibitor soon to enter man. A UK consortium is developing a multi-arm/multi-stage trial in collaboration with AstraZeneca to test their portfolio of DNA damage response candidates.

Proton Beam Therapy

In 2016 the NHS sent 210 patients to the USA and Switzerland for proton beam therapy at a cost of £114,000 each (compared with 136 in 2015 and 104 in 2014). Two proton beam installations in the UK, both considered national centres, are being built, with Manchester due to start clinical practice in summer 2018 (their cyclotron was delivered on 22 June!) via three gantries (plus a fourth research facility). University College London Hospitals (UCLH) will follow in 2021. The first priority is to repatriate patients who would otherwise have gone abroad before commissioning more “core” indications in paediatrics (particularly medulloblastoma) and adults (sarcoma, head and neck, selected cases of meningioma, orbital cancer, chordoma and other base of skull cancers) and then eventually adding evaluative trials for further indications. Once both centres are fully functional it is anticipated that 1500 patients will be treated per year (1% of current patients treated with photon radiotherapy, a far lower proportion than planned in Holland, for example). A 14 hour clinical day and total operation from 6am until 11pm each day will be in place with implications regarding contracts and many other logistical aspects. All patients will be consented and planned for both photon and proton therapy as a contingency and outcomes data will be collected for all patients. Specific clinical requirements such as exclusion of metal from the treatment area and how to maintain clear separation of the target site from neighbouring structures were discussed.

There are, of course, other single gantry commercial proton beam facilities coming on stream throughout the UK imminently. Whilst these are unlikely to be able to handle more complex cases, they are likely to create pressure on NHS commissioners to include a broader range of indications.

Clinical Management

The recently available relative wealth of clinical trial data in low grade gliomas still leaves many unanswered questions. For example:

- Which subset of patients do not benefit from chemo-radiation?
- How should one treat IDH wildtype patients?
- What is the optimal timing for initiating treatment for particularly indolent tumours?
- Can one delay treatment in order to reduce the cognitive deficit without loss in efficacy?
- Why does it take about four years before the survival curves of the best and poorer prognosis patients separate?
- Can one reduce or fractionate radiotherapy or ensure hippocampal sparing?
- Is proton beam therapy superior to traditional photon therapy?
- What is the impact of using chemotherapy alone on survival?
- Are temozolomide, PCV and nitrosureas equivalent?
- What is the impact of a neoadjuvant tumour lysate vaccine?
- Are IDH- or checkpoint inhibitors effective?

A number of other studies are in progress or opening imminently but the difficulty caused by long survival times means that valid surrogate endpoints are required. Those suggested were Progression Free Survival (but only if treatment does not alter vascular permeability), change in the rate of progression (if, in addition to excluding anti-angiogenic agents, one can measure this prior to initiating therapy) and response rate.

Of course, one also has to consider additional management factors and not just survival advantage, for example the psychological effect of providing patients with an estimate of projected survival possible if biopsy, and hence biomarker assay, has been conducted, or the reduction in seizures resulting from surgery and irradiation even if not associated with radiological or clinical response (although there is a suggestion that seizure response may be an early indicator of response to chemo-radiation).

Seizures are, of course, a common presenting symptom or may develop later, meaning that anti-epileptic agents are often given prophylactically with significant adverse effects. Hence, if as suggested by a study in meningiomas, existence of pre-operative seizures may be a significant predictor of post-operative seizures, it may be possible to withhold anti-epileptic drugs in some patients. Whilst seizures are less common in high-grade gliomas, it has been found that secondary, transformational high grade gliomas (as opposed to primary, de novo ones) and the presence of IDH mutation are associated with increased likelihood of seizure at presentation.

Increased survival in childhood cancer also comes with difficulties in follow up, whether of survival or of the many potentially significant long term side effects (neuro-cognitive, psycho-social, growth and development, organ dysfunction, fertility and reproduction, carcinogenicity) which may only become evident years after treatment. In the face of the current very limited evidence of their value in restoring subsequent fertility, a research study is underway in Edinburgh to carry out tissue and oocyte preservation in pre-pubertal children prior to their treatment.

The Elderly

The vast majority of the increased incidence of brain tumours is due to gliomas occurring in patients over 70 in whom there is poorer prognosis due to more aggressive biology (for example IDH mutation is rare and EGFR amplification common), frailty, co-morbidities, and issues with access to care. Fitness to treat is difficult to define and often only evident after the event. A number of studies in this age group have now been published and it was recommended that up to age 69 the aim should be maximum resection and chemo-radiation, and likewise in older patients who are MGMT promoter positive (or temozolomide alone if they can't tolerate radiotherapy). There was a call for a new study of chemo-radiation versus temozolomide alone after gross resection in MGMT promoter positive patients over age 70, although concern was raised in the audience as to the dramatic decline in performance status that can accompany craniotomy in such elderly patients.

Diet

In answer to the considerable interest shown in diet (the impact of lifestyle factors on survival was Number 1 in the list of priorities for research identified by the James Lind Alliance), two parallel multi-centre open-label Phase II randomised trials of the Modified Ketogenic Diet are due to open in patients with high grade gliomas receiving chemo-radiotherapy (the primary endpoint will be overall survival) and in patients with low- grade gliomas (primary endpoint: symptom levels). Many factors have had to be taken into consideration during trial design, including how to ensure that patients accept randomisation and do not self "prescribe", and the amount of dietetic support available.

Immunotherapeutics

Once it was realised that the CNS is not totally immune privileged, that leukocytes can traffic to the CNS and that there are lymphatics in the brain, it was natural to try to emulate the dramatic results achieved with immunotherapy (vaccines and anti CTLA-4, PD1 and PDL-1 checkpoint inhibitors) for metastatic CNS disease in melanoma and lung in primary glioma.

Prospective randomised double blind trials are now in place to study the dendritic cell vaccines in glioma with results from the DCVax trial expected in 12-18 months' time. [The outcome of the other study (ICT-107, utilising "off the shelf" rather than personalised antigens), may, however, be compromised or delayed as it has been reported that recruitment has been suspended whilst the company explores strategic options for further financing.]

Unfortunately the single peptide vaccine, rindopepimut, was shown to be inferior to the control arm but results from a Phase II study with the multi-peptide vaccine, IMA950, are awaited. The REO-Glio trial - which adds reovirus, an oncolytic virus and GM-CSF pre-treatment to standard of care chemo-radiation in adult glioma - will open summer 2017 at four sites.

Drug Discovery

Understandably perhaps there was competition between speakers as to whether it is surgery or radiation treatment that plays the central role in the management of patients with brain tumours. Current methods of drug discovery via genomics and identification of molecular targets are proving of no real success, whilst being very long and costly, and hence phenotypic screening via high throughput microscopy and stem cell technology, with target deconvolution only at a late stage, is now coming to the fore.

Clinical Trial Design

Medulloblastoma provides a master class in international collaboration to conduct effective trials despite there being only 650 cases per year in the EU (and 150 high risk cases). However achieving consensus means that time from concept to a trial starting is too long, especially as the design must be flexible enough to allow additional new therapies to be slotted in as they become available.

Unfortunately, the picture is not the same in adult brain tumours. Data from the NCRI Clinical Studies Group shows huge inequality across the country regarding access to brain tumour trials. Recruitment is challenging with barriers being, amongst others, resources, differing patient pathways, and lack of trials. The majority of patients don't remember their physicians speaking to them about possible trial participation and it was admitted that, when under time pressure in clinic, this may not occur. 26% of patients wanted to take part in a study but were unable to due to the lack of an appropriate trial or inclusion/exclusion criteria. 25% of potential patients are lost for preventable reasons e.g. distance from a participating hospital. In order to address this and recruit **all** brain tumour patients in the UK, **all** centres should take part in trials whereas currently many feel that the set up effort is not worthwhile if they are only likely to have a handful of appropriate patients.

Support

One particularly interesting report used evidence-based evaluation via geographic network analysis to identify areas of accessibility deficit (defined as >45 minutes travel time) to the support group network in Greater London, and highlighted regional disparities in access, with areas of concern being Bexley, Bromley and Croydon. Another, somewhat concerning, report centred on Stoke-on Trent, Staffordshire, Central Cheshire, Shropshire and Powys where the four Clinical Commissioning Groups in the immediate vicinity of the hospital are in the process of 'tendering out' Cancer Care and End of Life Care, consortia bidding for the two 10-year contracts with a combined value of £1.2 billion. This is necessitating working with all relevant parties to highlight the particular allied health practitioner needs e.g. occupational therapists, physiotherapists, speech and language therapists, dieticians and psychologists, of brain tumour patients.

Qualitative Research

A rather different (but again quite worrying!) topic listed all the different types of biases that can affect physician and surgeon decision-making and the advice they give to patients. It was recommended that best practice tumour boards, and not just multi-disciplinary meetings, be used to ensure that views of other similar specialists are taken into consideration.

Attendees were also introduced to the role of qualitative research via semi-structured, face-to-face interviews. Examples largely focused on patient satisfaction with awake craniotomy, gamma knife radiosurgery, "wait and see" management in low grade glioma, end of life care, or information provision prior to surgery, but this technique can also be used to elicit physicians' views e.g. how do they feel about elective surgical re-sampling of malignant tumours to guide treatment or do they (and the family) experience the loss of the relationship after their patient dies?

Conclusions

It is interesting to look back at the reports I have written after this conference in previous years and to identify trends. This year the scientific papers were thoroughly sprinkled with epigenetics, and everyone, scientists, surgeons and oncologists alike, were talking about the tumour margin and invasiveness!

Whilst we still have a long way to go to improve outcomes (the latest “great white hope”, immunotherapy is still a long way from proving fruitful!), there is a staggering amount of information available from ever more sophisticated imaging techniques, and biomarker classification and advanced radiotherapy modalities are allowing less aggressive regimes to reduce side effects.

Internationally, neuro-oncology must be congratulated on re-using clinical trial data to extract every last drop of information! One frequently heard results from repeated sub-group analyses of completed trials and there were more and more demands for new stratification factors to be built into trial design. However, much more needs to be done in the UK before recruitment of adult patients into trials emulates that achieved in paediatrics.

Management information (for example benchmarking data and qualitative research), long the domain of business, are now finding their place in medicine, and there is obviously room for thinking creatively as far as NHS cost constraints are concerned!

Appendix

The Young Investigator of the Year Award, jointly funded by BNOS and Brain Tumour Research, was made to Harry Bulstrode, University of Cambridge.

The best poster prize was awarded for “¹⁸F-methylcholine PET/CT, in vivo magnetic resonance spectroscopy imaging and tissue enzyme biomarkers of choline metabolism in primary brain gliomas” by Matthew Grech-Sollars (Imperial College, London)

The best scientific oral presentation was “A human iPS cell-based model of medulloblastoma demonstrates co-operativity between SHH signalling and mutation in an epigenetic modifier” by Jignesh Tailor (St George's University Hospital, London)

The best clinical oral presentation was “The impact of visual impairment on Health-Related Quality of Life (HRQoL) scores in brain tumour patients” by Sana Sharrack (University of Cambridge)

BNOS 2018 will be held from 4-6 July in Winchester.

Report prepared by Maryanne Roach on behalf of the BNOS Council and BNOS 2017 organising committee

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