



British Neuro Oncology Society (BNOS) Conference Report 2015

“Neuro-Oncology across the Ages” was held in Nottingham, England on 1-3 July. The conference opened with the Education Day which simulated the clinical challenges faced by multi-disciplinary teams (MDTs) in the young, adults, and the elderly. After that there were all the usual plenary sessions, including the Stephen Baker Memorial Lecture, proffered papers, posters and exhibitions by sponsors and, in addition, there was also a debate and filmed role play of consultations.

We were delighted to welcome as invited speakers:

Mr Henry Marsh (St George’s, London)	Prof. Jonathan Finlay (Columbus, Ohio)	Prof. Michael Weller (Zurich, EANO President)
Dr Simona Parrinello (Imperial College, London)	Dr Mathilde Chevignard (Hôpitaux de Saint Maurice, France)	Dr Katherine Warren (National Cancer Institute, USA)
Dr Helen Bulbeck (Brainstrust, UK)	Glenis Wilmot (MEP, East Midlands)	Dr Ralf Herold (European Medicines Agency)

We mustn’t forget, of course, another vital ingredient: plenty of opportunity for networking at the social functions (a reception at an Elizabethan mansion surrounded by a deer park – complete with lessons in how to shoot a long bow, an opera singer, and the conference dinner at which we were entertained by a band called “The Spinal Chords”).



This year all the presentations were filmed and they plus the abstracts, posters and presentation slides will be made available on the website. This report is intended to provide a flavour via some of the themes that stood out amongst the sessions that I attended.

Overall Incidence and Survival Statistics

The incidence of brain tumours is higher in both children and teenagers/young adults (TYAs) than in adults and a great variety of different tumour types are seen, with TYA patients tending to show better responses and longer survival than both children and adults. However, two thirds of children/TYA survivors have significant morbidity and diminished ability to acquire new skills due to the effect of treatment on the developing brain; 8-12% suffer from long-term radiation-induced malignancies. Many units have addressed this issue with dedicated 'late effects clinics'.

In adults, the number of cases of glioblastoma multiforme (GBM) and meningioma is increasing. A recent review of UK registry data published by the National Cancer Information Network Brain Tumour Group (Brodbelt et al European Journal of Cancer (2015) 51, 533– 542) shows that whilst 70% of patients with GBM are treated by means of radiotherapy after debulking, only about 35% manage to complete the Stupp chemoradiation regime. In the UK whilst time from diagnosis to surgery is on average 12 days, there are significant delays before initiation of radiotherapy/chemotherapy and there was a call for national standards to be devised to answer this.

The incidence of diagnosis of both GBM and meningioma has recently also nearly doubled amongst the elderly. Only 40%, or fewer, of elderly patients are actively treated, and few entered into trials, both due to poor initial performance status and the fact that they often subsequently decline too quickly to be assessed for active treatment, although it was stated that "if the patient can walk into clinic, we will treat them". Very few receive chemoradiation because patients over age 75 experience significant chemotherapy-related toxicity even if their initial performance status was good.

In both adults and the elderly, survival is improving slightly and survival is better if the patients have been actively treated (rather than having received purely palliative care).

Data Collection

Even though basic data submission to the National Cancer Registration Service is mandatory, more detailed research is hampered by inadequate reporting. For example, Chang staging is not reported in 40% of cases of medulloblastoma and data for brain tumours in children/TYA has only recently been reported by histological sub-type. Similarly, whilst the 'HeadSmart' campaign has resulted in a reduced total diagnostic interval (although there has been little impact on the patient portion i.e. from first symptom appearance to recognition of a possible problem by a medical professional), this interval data is still not reported to national registries in about 50% of cases. In addition, the now well-accepted importance of molecular markers has led to a call for this data to be collected



comprehensively in the Registry. This was exemplified in a comment “histology can have little or no association with detailed genomic diagnosis in Grade II/III gliomas” and the obvious importance of biomarkers in stratification and appropriate treatment of childhood medulloblastoma.

Extent of Resection

Interestingly, after the historical period during which the “Holy Grail” was gross total resection of IVth ventricle medulloblastoma, there is now established recognition that in these tumours, small residual volume is acceptable and may be prudent in the interests of reducing the devastating cerebellar mutism syndrome that currently affects 25% of cases, causing lifelong disability. Which measures will reduce this serious complication over the next few years are not established, although the design of current clinical trials may need to be re-considered if new strategies are introduced. One strategy presented was to use a pre-operative scoring system to identify those at greatest risk of this complication. Work still needs to be done on how to change the approach to diagnostic/ debulking surgery to offer a reduced risk of this complication for the child and predicting the risk may prove to be a first step to unlocking this dilemma for the surgeon.

On the other hand, gross total resection in ependymoma has been shown to be an independent prognostic factor for survival. Data from the early experience of a centralised review panel suggests that the panel might be more aggressive in recommending second look surgery than the clinician with responsibility for obtaining consent from the family. After devising an appropriate classification scheme, one study found that a central review panel would have re-operated in 64% of cases versus the 46% in whom second look surgery actually occurred. Hence the forthcoming SIOF trial will involve a centralised imaging and pathology review board (always including the surgeon who operated originally). It will be of interest to see how the central review recommendation and the actual surgery carried out compare as the process is further developed

Translational Studies

The spectre at any neuro-oncology conference is always the paucity of new treatments and fleeting signals of clinical efficacy shown by attempts to reverse this. The example of the dismal prospects for children with diffuse pontine glioma (DIPG) was used to call for the re-instating of non-human primate studies prior to Phase I trials (which should have an efficacy intent in future). Now that doing biopsies in children with DIPG, when authorised by ethical consent within trials or research institutions’ studies, and access to autopsy material, is becoming increasingly available, genomic studies have identified druggable targets and cell lines are now established. Recent research has discovered that whilst the histone deacetylase (HDAC) inhibitors eg panobinostat, are active in vitro and in animal models, extensive pharmacological study is still required to ensure that the drug gets to the target cell at appropriate concentrations to deliver the effect required in humans. Future clinical research is looking into the potential roles of convection-enhanced delivery and para-nasal administration.

Another presentation described work conducted to investigate whether the oncolytic virus, Reolysin, can be administered intravenously (rather than intra-tumourally) and the possibility of enhancing its effects by combining it with low dose GmCSF.

Meet the Experts – Tuberous Sclerosis Complex

The lunchtime workshop sponsored by Novartis discussed clinical presentations with this genetic condition which not infrequently presents in childhood with the benign sub ependymal astrocytoma (SEGA), requiring either resection or mTOR inhibitor therapy, and then later in life as benign kidney tumours and interstitial lung disease, especially in women. The case presentations emphasised the need for multi-disciplinary working and the need for specialist clinics to be established to advise on treatment selection and collection of outcome data.



Clinical Trial Design

Major ongoing trials were reviewed, particularly focussing on those studying bevacizumab in relapsed GBM (potentially a label changer), and those using the vaccines rindopepimut and ICT-107. Some disappointment was expressed that the controversial Novocure TTF-100A trial of electric field therapy had been terminated when a possible positive progression free survival had triggered a premature analysis of overall survival, allowing patients to crossover. As a result, no mature analysis of electric field therapy versus conventional therapy will now be possible in Europe although further trials in US may be considered. Further practical views expressed were that European patients would not embrace the wearing of this device, nor the considerable cost of the treatment be funded in the EU.

The European Medicines Agency (EMA) Innovation Task Force is exploring possibilities for adaptive trial design and basket trials (where the effect of a drug on patients with a particular mutation is studied, regardless of the site of the cancer) – although the EMA prefers controlled trials rather than a suggested N=1 database to collect case study data. The point was made that as a general rule patients seem to fare much better if they are entered in a clinical trial, regardless of the treatment arm: “It is almost unethical that more patients are not in trials”. There was a call for a closer link between the EMA and academic researchers and Industry.

The Clinical Trial Regulation will replace the European Clinical Trials Directive in 2016, bringing with it harmonisation across Europe, a single portal for submissions, mandatory uploading of results on a publicly accessible database* and a new category of “low intervention trials” (where the drug is used according to the Marketing Authorisation or off-label if following common practice). Unfortunately, though, the reduction in costs to companies that would have resulted from a scheme of national indemnification (instead of individual insurance) was not acceptable to sufficient EU member states. This is a pity as currently very large insurance premiums are being made for minimal compensation payout.

* Bearing in mind that there will soon be total transparency of results from drug trials, it was interesting to hear it said that trials of surgical procedure are not published/publishable unless superiority over current practice has been demonstrated!

The James Lind Alliance (JLA) has utilised a sophisticated cross community approach to identifying the top 10 clinical research priorities:

James Lind Alliance Top 10 Priorities (relating to patients of any age) June 2015

1	Do lifestyle factors (eg sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?
2	What is the effect on prognosis of interval scanning to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?
3	Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
4	In second recurrence glioblastoma , what is the effect of further treatment on survival and quality of life, compared with best supportive care?
5	Does earlier referral to specialist palliative care services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumour?
6	Do molecular subtyping techniques improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumour?
7	What are the long-term effects (physical and cognitive) of surgery and/or radiotherapy when treating people with a brain or spinal cord tumour?
8	What is the effect of interventions to help carers cope with changes that occur in people with a brain or spinal cord tumour?
9	What is the effect of additional strategies for managing fatigue compared with standard care, in people with a brain or spinal cord tumour?
10	What is the effect of extent of resection on survival in people with a suspected glioma of the brain or spinal cord?



Consent

Subconscious cognitive bias (to which both surgeons and patients are subject when discussing risk) was demonstrated, using the example of the manner in which surgical treatment options, specifically for low grade glioma, are described. For example, resection of insular tumours carries a significant risk of a major stroke and, whilst awake craniotomy can prevent damage to eloquent areas with reduced risk of focal neurological deficit, post-operative changes in personality and problems of social interaction may still occur as they cannot be detected intra-operatively. Recent case law has altered demands made of doctors when obtaining consent, this now being judged more from the patient's perspective. The suggestions were made that specialists' letters to GPs (which are copied by many units to patients) should include the reasoning behind clinical decisions and that special care needs to be taken to document everything in contemporaneous records.

Filmed roll-play was used to demonstrate how (and how not!) to break bad news at an initial consultation, the material that is available to assist patients prepare all the appropriate questions in advance were enumerated and the suggestion made that patients might be encouraged to record this meeting on a smartphone. It was reported that many patients cover up the fact that they don't understand what they have been told; furthermore, recent work would suggest that 25% of patients coming to surgery don't have the capacity to have made the decision.

Rehabilitation

A major focus in the conference was rehabilitation and impressive long term in- and out-patient rehabilitation, education and treatment facilities available in Paris were described. UK speakers stressed current inadequacies, and new therapy models in development were described.

Comparison with Europe

A new entrant into the programme was a debate using the "Question Time" format chaired by Dr Peter Homa, CEO Nottinghamshire University Hospitals NHS Trust. The panel (Jacqueline Cornish, Garth Cruikshank, Paul Grundy, Kathy Oliver, Geoff Pilkington and Michael Weller) answered questions posed by the audience on the topic: "Are brain tumour services in the UK comparable to the rest of Europe?" There were several aspects of treatment in which the UK was thought to be superior to the rest of Europe, namely the use of MDTs (although there was a call for their work to be audited), availability of specialist nurses, the well-developed charity sector and its impact on decision-makers, and the existence of mandatory data collection. However, we were thought to be lagging behind in terms of diagnostic procedures, surgical technologies (for example, lack of funding for use of 5-ALA), use of post-operative MRIs, and patient recruitment into clinical trials.





British Neuro-Oncology Society

Best presentation and poster prizes were awarded to Ruman Rahman (University of Nottingham), Matt Baker (University of Strathclyde), Rebecca Lewis (N Bristol NHS Trust), Kate Hollingshead (University of Birmingham), and Durga Sabnis (Children's Brain Tumour Research Centre, Nottingham).

The conference promoted a very positive and interactive atmosphere where widespread discussion across the scientific, clinical and community-based groups took place and achieved a significant enhanced consensus of the challenges facing those that treat, research into, or support patients of all ages experiencing a brain tumour or the aftermath of such experiences.

Council would like to acknowledge the hard work of the Nottingham CBTRC team led by Professor David Walker, with Beth Coyle and Donald MacArthur leading the programme development, Jenny Loughlin supporting the scientific committee, Lisa Storer and Sue Franklin leading the administration, and Ruman Rahman and Stuart Smith leading the sponsorship and social programmes.

BNOS 2016 will be held from 29 June to 1 July in Leeds.

Report prepared by Maryanne Roach on behalf of the BNOS Council and BNOS 2015 organising committee

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