British Neuro-Oncology Society

British Neuro Oncology Society (BNOS) Conference Report 2016

Approximately 250 people with an interest in neuro-oncology attended part or all of "Trials, Technologies and T-cells" in Leeds from Wednesday 29th June – Friday 1st July 2016. The conference opened with the Education Day during which five sessions consisted of paired presentations made by scientists and clinicians. After that there were plenary sessions, including the Dr Mary Catterall and Stephen Baker Memorial Lectures, proffered papers, posters, a special session for allied health professionals (discussing fatigue), and lunchtime seminars and exhibitions by sponsors. BNOS was pleased to award bursaries to five younger applicants.

Of course the social and networking opportunities were not ignored with a Welcome Reception at Leeds City Museum and the Conference Dinner taking place at the Royal Armouries Museum (after a most entertaining demonstration by two knights in medieval armour!)

Council would like to acknowledge the hard work of the Leeds team led by Professor Susan Short. As the strap line to the Conference title predicted, they certainly brought together the best of basic science and clinical research in neuro-oncology.

We were delighted to welcome as invited speakers: Bernhard Radlwimmer (German Research Center), Laura Evgin (Mayo Clinic), Nicola Sibson (Oxford Institute for Radiation Oncology), Stephanie Combs (ISAR Hospital, Munich), Richard Gilbertson (University of Cambridge), Luisa Ottobrini (University of Milan), Gelareh Zadeh (University of Toronto) and Sebastian Bradner (University College, London).

The plenary sessions were filmed, and will be made available on the BNOS website, and attendees received abstracts of the proffered papers and posters via USB stick. 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.

Methodological Techniques for Assessing Efficacy

Many presentations revolved around the set up, testing and quality assurance of novel assay techniques designed for in vitro or pre-clinical use. These included the use of mathematics to model drug release/take up from a polymer particle paste intended for intra-cavity implantation and the design of microfluidic chips which should maintain tissue viability/cancer cell proliferation hence allowing practical and cost effective testing of therapies in a near natural environment.

To date a desire to use arterial spin labelling (ASL) as a non-invasive MRI technique to quantify perfusion has been hindered by inconsistent results in pre-clinical experiments so considerable work has been done to reliably determine changes in tumour perfusion in a rat model of brain metastasis.

Further developments are still required, however, when studying CNS metastasis, pre-clinical research being hindered by the lack of good models. In vitro techniques cannot reflect the tumour micro-environment and reliance on spontaneous development of metastases in animals is impractical [except in melanoma where, as in humans, a high incidence makes this feasible], although xenografts in a new strain of immunocompromised mouse are an improvement (but still taking up to nine months for metastasis development). Another option being tested is that of seeding tumour cells onto brain slices.

An innovative concept is being used in Cambridge whereby the multi-disciplinary team (MDT) concept has been transposed to the laboratory and candidate drugs are tested in mice in conjunction with surgery and radiotherapy in near-human randomised trials.

Metabolism

Everyone is trying to understand the many altered metabolic pathways in cancer cells and ubiquitous regulatory mechanisms. Due to the limited effectiveness of targeted therapies due to the inherent heterogeneity of glioma, an attractive alternative strategy is to exploit the altered metabolism exhibited by virtually all tumour cells i.e. their high dependence on glucose [Note: this reliance upon glycolysis has recently been called into question]. Theoretically, this can be accomplished using the therapeutic ketogenic diet (which potentially reduces the supply of glucose to tumours by providing very low levels of carbohydrate and 75% fat); anecdotal reports suggesting that it might potentiate the effects of chemotherapy and radiotherapy. Studies in mice suggest that the diet results in general upregulation of microRNAs with a tumour suppressor function similar to those in normal brain.

It has also been shown that the glycolytic enzyme hexokinase 2 (HK2) is crucial for the Warburg effect, and as it has little or no expression in normal brain, it is an attractive target for targeting. However, in the absence of a known direct inhibitor, exploration of gene networks regulated by, or associated with, HK2 was necessary and has led to the identification of the azole class of antifungals as potential inhibitors of tumour metabolism.

Genomics & Biomarkers

The Genomics England 100,000 Genome Project for rare conditions and cancer launched in 2013 (whole genome sequencing accompanied by clinical context) has, since May 2016, been extended to include adult gliomas and specified other brain tumours, with a sample allocation of 1000. Attendees were encouraged to open communication with one of the 13 local NHS Genomic Medical Centres which are responsible for extracting DNA from samples and forwarding it to Cambridge for sequencing (at no local cost). It was admitted that the lengthy consent form is an issue but the data is expected to fuel many useful analyses.

Next generation sequencing is, of course, now central to research and diagnosis, and will be in the future for choice of personalised therapeutics; streamlined paths are being devised to identify the relevance of the very large chromosomal copy number changes seen in brain tumours. Many speakers described the identification of particular genetic mutations present in sub-groups of specific brain tumours, with some evidence of differential response to treatment eg in paediatric high grade gliomas and medulloblastoma.

The PARADIGM trials focus on the premise that “cells with stem-like features” upregulate the protein responsible for repair of radiotherapy-induced DNA damage. This potentially can be reversed by a poly ADP ribose polymerase (PARP) inhibitor, with optimal radio-sensitisation occurring when combined with an ATM kinase inhibitor.

A unified and simplified classification of gliomas is now possible by combining histopathological features (i.e. what is recognised through the microscope) and molecular biomarkers. Some of these molecular biomarkers (such as the IDH mutation and the ATRX loss) can be easily tested with antibodies (a routine practice in all pathology departments) whilst other markers such as the TERT promoter mutation and the 1p/19q loss require a molecular pathology set up, which is not available in all centres. The new 2016 WHO classification is a major step in recognising the importance of these biomarkers for clinical diagnostics and for patient stratification for optimal treatment.

Imaging & Radiotherapy

As full molecular characterisation is not yet routinely available in clinical practice, greater demands are being placed on traditional diagnostic techniques. The deduction of IDH mutation status from MR imaging and spectroscopy can perhaps be made by study of degree of contrast enhancement, oedema, sharpness of margins, path of growth, blood vasculature and build up of 2-hydroxy glutarate. In medulloblastoma an imaging agent taken up preferentially by the leaky vasculature is being developed so that the good prognosis ‘wingless’ **(**WNT) subgroup can be identified

on MRI, possibly precluding the need for total resection and thereby possibly reducing the risk of posterior fossa syndrome.

70-80 % of neuro oncology patients are treated by means of radiotherapy but the potential of radiotherapy delivery techniques is greater than the accuracy of target definition; there is enormous planning variation between oncologists (although improved somewhat by concomitant use of PET scanning). Hence attempts are being made to fuse CT with MRI, rather than as two separate radiotherapy planning procedures, or to use an MR-integrated LINAC so the patient doesn't have to be brought in for a prior planning session at all. And as immobilisation can only currently be controlled to within 3 mm, there are also attempts being made 3D print the mask from the MRI. The INSERT (INtegrated SPECT/MRI for Enhanced Stratification in Radio-chemo Therapy) project has as its objective the development of a multi-modality imaging tool for concurrent spectroscopy and MRI.

Better MRI diagnostic techniques are also required to detect CNS metastases at an earlier stage and as markers of early response to treatment. Several groups are investigating optical imaging by means of bioluminescence and fluorescence. For example, hypoxia inducible factor 1 (HIF1)-mediated luciferase activity has been shown (in experimental models) to be proportional to cell proliferation and tumour growth and may be more sensitive than positron emission tomography (PET).

Diffusion tensor MRI (DTI) and geomechanic techniques are being used to measure the disrupted white matter tracts through which infiltration occurs with a view to redefining surgical targets and allowing personalisation of radiotherapy treatment volumes. A surgical study will open later this year comparing the 5-ALA fluorescent area with the DTI area as it has already been shown that there is far better correlation between cell proliferation and 5-ALA fluorescence than with traditional contrast enhancement.

Immuno- viro therapy

Despite the original belief that the CNS is immune privileged, now it has been shown that an active immune response against intra-cranial tumours can be generated there has been a rapid move into various types of immunotherapy: vaccines, oncolytic viruses, checkpoint inhibitory monoclonal antibodies, and adoptive cell transfer with chimeric antigen receptor (CAR) T cells. The great variety of mechanisms of action and targets ensures that an enormous number of combinations are possible, both with other immune-mediated therapies, of the same or different class, and with conventional chemo radiotherapy.

Particular attention was given to:

- ICT-107, a dendritic cell vaccine (as an aside, another research avenue being explored is the possibility that circulating myeloid dendritic cells may be more effective than peptide vaccines and laboratory-generated monocyte-derived dendritic cells.)
- Reovirus, an oncolytic virus (which self amplifies its dose specifically at the target cancer and not in normal cells) in Phase I/II in paediatric high grade glioma and in combination with standard of care chemo-radiation in adult glioma. It was originally administered intra-tumourally but intravenous administration is now possible along with GM-CSF pre-treatment. There is also interest in convection-enhanced delivery via micro-catheter in diffuse intrinsic pontine glioma (DIPG).
- Nivolumab, ipilimumab and other checkpoint inhibitors being used alone or in combination in the portfolio of so-called Checkmate clinical studies – although it was emphasised that there is a need to monitor patients carefully and intervene early if there are side effects.

Immunotherapy is another area where traditional endpoints are of limited value. There is a chronological disconnect between active cellular response (which may occur within a week) and clinical tumour response (unlikely to be

evident for weeks or months) and, in any case, there is concern as to whether peripheral response is necessarily indicative of intracranial activity. In any case, the various types of assay still require harmonisation and standardisation, and the nature of the dynamic immune response is reflected in same-patient variations on different days. In addition, there may be an initial increase in tumour burden due to infiltration by immune inflammatory cells, an indicator of antitumour response, but which could be considered progression using traditional methods of assessment. These issues are being addressed by the newly devised Immune-related Response Criteria (irRC), but the fact that no single biomarker of immune response is ever likely to be available means that other types of assessment such as neuro-oncology-specific Patient Reported Outcome Measures (PROMs) need incorporation.

Clinical Advances

Attempts are being made to translate improvement in diagnosis time in children to the adult setting with a "Headache Plus" initiative which incorporates guidelines for identifying headache suspicious of cancer, co-existence of subtle behavioural or cognitive symptoms (possibly using a simple fast semantic verbal fluency screen done in the GP clinic), a past history of cancer, and visual signs confirmed by optometric evaluation of visual fields and fundi.

Initiatives like this are bringing more elderly sufferers into the potentially treatable pool and whilst there is a gradual increase in active treatment of these patients as prognostic factors are elucidated, there is currently very little cognitive/frailty screening to predict their tolerance to therapy - although those practitioners who do utilise such assessments find the results of value in making treatment decisions. As a result, there were calls for a multidisciplinary Geriatric Assessment tailored specifically for use in neuro-oncology.

Although there are not yet even any proton beam installations in the UK, it was of interest to hear of carbon ion therapy in Germany, particularly for highly radioresistant tumours like chordoma, and the imminent CLEOPATRA (carbon ion therapy versus proton in primary glioma, both combined with Standard of Care treatment) and CINDERELLA (carbon ion therapy vs fractionated stereotactic radiotherapy in recurrent/progressive glioma) trials.

Also outside the UK, there are issues of patient compliance and limitations on voltage intensity with the Optune™ system, currently available in the USA and some other parts of Europe, which may be addressed by means of implantable deep brain stimulation electrodes to deliver therapeutic electromagnetic fields.

CNS Metastases

Research is becoming ever more important in this field as the number of patients with CNS metastases is rising dramatically due to demographic trend and better management of primaries; MDTs are reporting more patients with good performance status and less advanced primary disease. Where tumour location allows, open surgery may be the quickest way to reduce pressure symptoms but the recent reorganisation of stereotactic radiosurgery (SRS) services within NHS England should mean that all appropriate cases (KPS >= 70, total volume <20cc (irrespective of number of metastases) and prognosis > 6 months) now have access to single or fractionated SRS locally. One major hospital, though, reported that, despite a large increase in total referrals, the number of patients accepted by the MDT for specialist intervention (neurosurgery or SRS) had not increased, due to lack of data on performance status, estimated prognosis, or nature of the primary in the vast majority. Better education of referring physicians as to the NICE guidelines regarding CNS metastatic disease may be called for.

The point was made that clinical trials in CNS metastatic disease are very difficult to devise due to lack of appropriate endpoints caused by the impact of extra-cranial disease (e.g. pseudoprogression associated with its treatment), as well as poor compliance when life expectancy is limited.

Biopsy & Tissue Banks

Day case image-guided biopsy, usually under local anaesthetic, has been carried out in Southampton since 2006 for appropriate outpatients living with another responsible adult and when it is possible to finish the operation during the morning. As long as a CT scan after 4 hours reveals no haematoma, the patient is then discharged after 6 hours. In the 9½ years, 55% of 645 biopsies performed were day case and 92% of those were discharged the same day. However others commented that the suitability of patients is likely to be dependent on the hospital catchment area.

Cost savings, as well as patient satisfaction, are also being driven elsewhere by a nurse-led follow-up telephone clinic. Follow-up scans are undertaken locally and viewed remotely, the consultant discussing plans with the Specialist Nurse prior to the telephone appointment.

The joint Walton-Preston Research Tissue Bank has over the period 2011-2015 released 470 tissue samples and 267 blood samples all with associated clinical data. Since 2015 tissue and blood samples have been matched and 27 projects have been supported. An electronic consent procedure has now been developed. In future a charge will be made to cover administrative and maintenance costs. By contrast, BRAIN UK (the National Brain Tumour Bank Network) is a virtual tissue bank with tissue retained by participating centres and the final decision as to provision being theirs (although ethics approval is obtained centrally). Originally BRAIN UK only included post mortem tissue (covering all types of neurological disease and not just neuro-oncology) but has more recently been extended to include residual surgical tissue. 26 out of 81 applications were supported over the period 2010-2016, with over 3,000 tissue samples approved for release for research. 19 studies have resulted in publications.

Conclusions

It is not saying anything new to emphasise the enormous challenge that we face. We are not short of ideas – rather the opposite. There are a vast number of hypotheses as to the basis for the heterogeneity and plasticity of glioma, and its invasive and migratory capacity. In addition, there are many (cause or effect?) inter-relationships between genomics, proteinomics and metabolomics, and the impact of the tumour on normal brain metabolism and, vice versa, the effect of the tumour's micro-environment to be considered. There are a plethora of putative treatment targets .... but we still seem so far off significant clinical progress.

And one could be forgiven for thinking that the advent of genomic screening has made this even worse by characterising more and more genetic lesions and aberrations requiring investigation, although we are at least able to better predict prognosis and response to current treatment in some tumours on the basis of these molecular variations.

Of course, it is easy to forget that before this research can progress, the innovative assay, imaging or modelling methods themselves have to be developed and require optimisation and standardisation.

Our search for the answer has us dancing to and fro. On the one hand, there is the search for ever more specific and highly targeted, personalised therapies (that the NHS may never be able to afford?) whilst, on the other hand, the heterogeneity of the disease soon renders these ineffective, meaning that research either moves back to broader epigenetic strategies or devises ever more complex combinations of modalities with differing and, often cascading, mechanisms of action.

Appendix

The best presentation prize was awarded to Dr Jason Adhikaree, Nottingham Enhancement of Myeloid Dendritic Cells through MAPK p38 inhibition Promotes T cell Proliferation and Restores Adaptive Immunity in GBM Patients

The best scientific poster was by Chiara Moriconi, Cardiff University/ School of Pharmacy and Pharmaceutical Sciences Caveolin-1 implicated as a pro-invasive gene in high-grade glioma cell models: Implementation of a 3D spheroid matrix invasion assay

The best clinical poster was that of Ingela Oberg, Cambridge University Hospital NHS Foundation Trust (Addenbrookes) Nurse-led telephone clinics improve patient satisfaction and enhance follow-up for benign / low grade tumour patients

BNOS 2017 will be held from 21-23 June in Edinburgh.

Report prepared by Maryanne Roach on behalf of the BNOS Council and BNOS 2016 organising committee

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