Analysing the Past to do Better in the Future
The European Association of Neuro-Oncology (EANO) Conference
Turin 9-12 October 2014

Nearly 1000 healthcare and allied professionals (including many "big names" from both sides of the Atlantic and beyond) attended the biennial EANO meeting which was held in the Lingotto Conference Centre in Turin, Italy, part of the converted former Fiat factory. This was constructed in the early 1900s, the design being unusual in that it had five floors, with raw materials going in at the ground floor, and cars built on a line that went up through the building. Finished cars emerged at rooftop level to go onto the test track (which featured in the film "The Italian Job" and is still there). However, the other thing for which this city is particularly famous, the Turin Shroud, was not available for viewing.

The conference opened with an Educational Day consisting of parallel clinical and laboratory science sessions, both having an emphasis on CNS metastasis. We mustn't forget that whilst GBM (glioblastoma multiforme) is still a major challenge, approximately 40% of brain neoplasms are actually secondaries from other cancers eg lung, melanoma, breast etc, and these are an increasing problem as patients live longer due to treatments for the primaries becoming more effective. Although there are no exact data, one speaker cited brain "mets" as affecting 6% of the population. There were then another 2½ days with up to four sessions running concurrently, including nursing and quality of life topics, evening satellite symposia sponsored by various companies, and poster viewings.

Reverting back to GBM, in recent years, several large Phase III clinical trials have failed to show superiority (in terms of overall survival) for the new compounds being evaluated. However, there is still much analysis being conducted to investigate other key features such as quality of life issues and effect on steroid dosage, as well as whether particular sub-sets of patients may benefit from the treatments. These trials are massive undertakings with enormous costs so it is recognised that they should be designed to create as much information as possible and that lessons are learned from the previously unrecognised implications of particular facets of each trial's design.

Dr Roger Stupp (Switzerland) presented a very valuable and frank retrospective critique of the cilengitide trial (CENTRIC), in the development of which he'd been instrumental. There had been excellent collaboration between EORTC (European Organisation for Research and Treatment of Cancer) and the sponsoring company but in hindsight he felt that some aspects of the trial could have been different. In general, he called for even greater and earlier industry-investigator collaboration, trials designed to identify failure earlier, and clear planning with go/no-go decisions adhered to at each stage. There was a call for publication not only of results from all trials but also of the detailed protocols that were utilised so that the results can be better understood.

The other two trials referred to above focussed on bevacizumab (Avastin) and although this therapy is not licensed for use in Europe clinicians still find tantalising suggestions of activity at recurrence. Hence there are a number of trials being conducted of various bevacizumab combinations in recurrent disease and, interestingly, the suggestion that a lower dose may produce better outcomes. There has been a re-emergence of interest in an older chemotherapy, lomustine (CCNU), in combination with bevacizumab at recurrence.

Chair and Co-Director: Kathy Oliver, PO Box 244, Tadworth, Surrey KT20 5WQ, United Kingdom. Tel: (44) (0) 1737 813872, Fax: (44) (0) 1737 812712, Mobile: (44) (0) 777 571 2569. Email: kathy@theibta.org

There will also be a US trial to see if the Novo-TTF device can be used successfully in combination with bevacizumab after failure of the single agent therapy. Novo-TTF is a treatment approach in which the patient wears transducer arrays on his/her shaved head continuously throughout the day in order to expose the tumour to "wave-like" electric fields called "tumour treating fields". Patients using this device will be glad to know that a new device half the size and weight will hopefully be available next year.

Whilst further developments in clinical trial design are still needed, it was noticeable from the presentations that smaller but comparative Phase II trials are now being utilised to a greater extent, hopefully ensuring that "signals" of therapeutic efficacy in particular groups of patients can be identified faster and at lower cost. It was also recognised that there must be flexibility to amend a trial design (the so-called "adaptive trial" approach) whilst running a study as new data becomes available, and whilst still maintaining data integrity.

A significant challenge in trial design can be "crossover" (when the patient involved in a clinical study of two treatments is given one until tumour recurrence and then given the other in the hope of further response) because this can confound interpretation of the ideal endpoint i.e. overall survival.

Although the best currently available treatments for patients with some types of brain tumour are widely accepted (even though everyone knows that better ones are still required) there are still many brain tumour types for which there is not yet a "standard of care". It was interesting, therefore, to hear presentations from France and Germany as to their slightly differing approaches to the treatment of anaplastic glioma. There were also presentations explaining the meticulous projects being run by EANO working parties to draw up guidelines as to how each type of brain tumour may be treated, based on carefully analysed evidence and in-depth discussion amongst experts where no high quality data yet exists. (One objective of this work is to assist countries when seeking reimbursement for novel treatments). It was stressed, however, that clinicians and surgeons must still discuss with their patients the options, agree functional boundaries, particularly when surgery affecting "eloquent" areas is concerned, and agree any trade-off between survival and quality of life.

It is now preferable that patients are stratified, whether or not they are taking part in a trial, according to various molecular or genetic biomarkers as there are a number of instances where the patient's status in this respect is known to affect the likely course of their illness or their response to treatment. In trials, results must be analysed for each sub group separately. Indeed, where a link has been identified, there are trials underway which focus only on patients with poor prognostic biomarkers so as to try to find a treatment particularly applicable to them. There is a major European initiative (the EORTC's SPECTA platform) in which patients are pre-screened so that, even if not immediately available, if a new trial opens that is appropriate to them there is no delay while screening is done. The IBTA included an article about the SPECTA platform for brain tumours in its 2014 magazine – an electronic copy can be read here: http://issuu.com/ibta-org/docs/ibta-2014

Utilisation of molecular classification is also aiding development of the new WHO (World Health Organisation) classification for brain tumours (which is expected to come into use in Spring 2016). The suggested layering of traditional histological definitions with these new determinants has been likened to the method used by Google maps. Some "mixed" diagnoses will disappear as the additional molecular results will allow them to be placed in one or other of the more definitive groups.

As immunosuppression is a critical factor in GBM, it is hardly surprising that there are many forms of immunotherapy being studied including so-called "checkpoint inhibitors". It is thought that cancer cells may hide from the immune system and shield the tumour from immune attack by speeding up the production of "checkpoint proteins" and that checkpoint inhibitors (eg nivolumab, ipilimumab) may stop this from happening. These agents are already holding great promise in melanoma, showing that major advances in treatment of highly challenging diseases **do** happen so we hope that GBM follows suit. Another interesting avenue discussed was that of vaccines; combinations of vaccines and checkpoint inhibitors are also being tested.

There were a number of presentations at EANO Torino regarding seizure control in low grade gliomas. An interesting possibility is that antiepileptics may possess some tumourigenic activity and that some chemotherapies may reduce seizures by reducing tumour-derived pollutants, even without measurable effect on the tumour itself. There appears to be a tendency towards earlier surgery in low grade gliomas as a means of controlling epilepsy and, some would argue, overall survival, and the rate of alteration in volume of low grade gliomas can now be used to judge likely time to malignant transformation.

The fact that there are now a number of trials specifically for elderly patients, who have previously been excluded from clinical studies, was welcomed.

Of course, it is not only drugs that need to be carefully tested. This is also required when deciding on surgical technique, interpretation of MRI (magnetic resonance imaging) scans, assay techniques for biomarkers etc. As an example, the mainstay of diagnosis and follow-up - the MRI scan - became difficult to interpret when the phenomena of pseudo progression and pseudo response were identified. As a result, new definitions of radiological response had to be derived (RANO - Response Assessment in Neuro-Oncology) and great care is now taken in the appropriate timing of scans to take these artefacts into consideration.

Prof Michael Brada (UK) continued this theme in his excellent and highly accessible keynote lecture. He reviewed some of the new cutting edge technologies and scheduling available for delivering radiotherapy, concluding that there is currently little evidence of better clinical outcomes and said that prospective testing is required. He was one of several speakers to allude to the recent high profile UK case about proton beam therapy, explaining that there is not yet evidence of therapeutic efficacy or even confirmation of the theoretical suggestion of reduced side effects when compared with traditional (photon) radiotherapy.

Despite excellent cross-border organisations such as the EORTC and RTOG (the US NCI-funded Radiation Therapy Oncology Group) there is still greater need for international collaboration in order to design and conduct trials that follow a logical, stepwise progression of information gathering without duplication of effort. The example was given of CERN (the Collaborative Ependymoma Research Network) which links 18 US centres for purposes of clinical trials, centralised tissue collection, in vitro candidate testing and animal model development. CERN also embraces social media and has developed a Wikipedia page and an Ask the Expert website forum.

The full day Nurse Session at EANO Torino was very well attended and simultaneous translation from and into Italian was provided at this EONS (European Oncology Nursing Society) approved event. The quality of the presentations was excellent and included topics focussing on the needs and experiences of brain tumour patients; how to manage antiangiogenic treatments and clinical trials; patient/spouse relationships; communication between doctor, patient and caregiver; rehabilitation; awake craniotomy; epilepsy; and the role of physiotherapy for brain tumour patients in the hospital setting. Another presentation highlighted long term survivorship of high grade glioma, describing it as “a new reality” in the world of neuro oncology, which brings with it, on the one hand, new challenges in terms of care and support and on the other hand, provides hope for those diagnosed with this most devastating of diseases.

Patient advocacy organisations were also in evidence at EANO. Two of them - Brain Tumour Research (UK) and Deutsche Hirntumorhilfe - as well as the International Brain Tumour Alliance (IBTA) - had display tables. A side meeting organised by the IBTA for leaders of Italian brain tumour patients’ groups (Associazione Italiana Tumori Cerebrali, Il Fondo di Gio, BrainLife and Italia - Glioblastoma Multiforme - cancro al cervello) also took place at EANO Torino at which challenges and solutions in the brain tumour patient and caregiver communities in Italy were discussed.

Although no world-shattering, new clinical data was presented at EANO, we should be optimistic that research is now more logically targeted and that we are making the most of the recent past to become more fleet of foot and savvy in the future.

Maryanne Roach
IBTA Science & Technology Adviser