“Contemporary Approaches to Paediatric and Adult Brain Tumours”, held in Liverpool, England 9-11 July was, with its best ever attendance of 350, a very professionally organised and interesting conference - an excellent demonstration of the heightened awareness of neuro-oncology, also noted in a number of local media interviews.

The opening Education Day provided parallel sessions for scientists and clinicians, the informal attitude encouraging plenty of interaction. One track focussed on molecular characterisation – a theme which ran throughout the conference. The other comprised presentations of interesting and challenging cases complete with history and radiology, following which the audience were invited to vote on the various options for management before a member of the “MDT” panel succinctly presented the literature and clinical trial evidence to back up their recommendation.

Parallel sessions continued throughout the main meeting, also ensuring that there was plenty of interest for the nursing and allied healthcare professionals wanting to cover topics such as rehabilitation, epilepsy and Quality of Life measures. There were all the usual plenary sessions, proffered papers and posters, and exhibitions by sponsors.

I was naturally unable to attend all the sessions – and probably wouldn’t have understood much of the deep science – but I have picked out some of the themes that stood out to me.

Incidence and Survival

The National Cancer Intelligence Network (NCIN) has now published data from 2007-2011 which includes 10,743 new cases of glioblastoma multiforme (GBM), at 4.1/100,000/year higher than in the USA and level with the highest European countries. Over 90% of cases have histological confirmation. Incidence increases with age and is slowly increasing. Median survival is 6 months, 28% survive for 1 year and 11% for 2 years. Median survival for those over 50 is < 1 year and for those over 60 is < 6 months. 61% of the youngest age groups survive 1 year.

The best survival occurs when patients have all three modalities of treatment, surgery, radiotherapy and chemotherapy (median 14.8 months if less than 70 years old). Maximal treatment increases survival in all ages but only 34% had maximal therapy and this reduces with age. It was pointed out that there are a large number of patients eligible for maximal treatment that are not going into trials (also see below).
But does more rapid diagnosis always result in better overall survival? Data was presented for a series of 118 patients with newly presenting high grade glioma treated at the National Hospital for Neurology and Neurosurgery, London in 2011. 80% presented as emergencies (even higher than the NCIN’s reported 60%) even though there was no difference in symptoms at presentation. Those that presented at Emergency were diagnosed more quickly (8 days vs 26 for those that presented at Outpatients). Paradoxically, earlier diagnosis equated to worse overall survival (OS 181 days vs 386), presumably because rapid symptomatic deterioration necessitating emergency admission is a poor prognostic factor not influenced by earlier diagnosis and treatment.

**Clinical Trials**

Over and over again, presenters commented that there were no trial data to prove whether a particular treatment was or was not superior to others .... or described in detail the problems associated with agreeing appropriate endpoints or other challenges of clinical trial design.

Comparison of trial results, even those purporting to use the same regimes, is made difficult by dosage variation and differences in radiotherapy regimes between centres, and particularly from one country to another. For example, in Europe and the USA procarbazine, lomustine/CCNU and vincristine (PCV) is given in higher doses than in the UK for oligodendrogliomas.

The CODEL study was so long in discussion that it has most probably been overtaken by the 10 year follow up publications from the EORTC and RTOG showing a long Overall Survival advantage in the 1p 19q co-deleted sub-group of oligodendroglioma patients treated with PCV. As a result, the USA is now treating these patients with the Stupp regime due to lower toxicity and ease of administration even though there is no clinical trial evidence for its efficacy.

The Ependymoma II study has taken 8 years to develop; is the complexity of trying to answer too many questions in one study slowing down design (although with patient numbers so low it is, of course, understandable that investigators want to make the most of every cohort.)

Whereas in 2011 there were only 13 glioma and 8 non glioma trials in the NCRI portfolio, in 2014 there are 17 and 18 respectively. If a patient has a Performance Status (PS) of 0/1, there is a trial for every type of brain tumour. However, the majority of these trials are academic (as are all interventional studies), very few are from Industry, and none have been developed in partnership. This lack of interaction between research centres and Industry is disappointing. Recruitment to interventional trials remains poor even though the number of studies available is now comparable to that in other tumour types. It was felt that the existence of too many sites in the UK hinders recruitment because of the high administration cost per site. However further centralisation was considered politically impossible. The NCRI Brain Tumour Clinical Sub Group is continuing to focus on trial development, but also on molecular stratification and setting up a network for preclinical testing and of early phase trial centres.

In Cambridge 25% of potential patients are lost for preventable reasons: 16% due to geography and travel costs, 5% because of problems with scans and 4% due to time constraints re protocol. A nationwide study has shown that barriers, according to staff, are resources, patient pathway and availability of trials. However, when questioned, patients don’t remember being asked if they wish to participate in a trial – or believe that no suitable trials are available. Because brain tumours have such a bad prognosis, the nihilistic attitude must be replaced by one of doing the best possible i.e. ensuring participation in trials wherever possible. It is commonly thought that patients will not take part in a trial where they may be randomised to receive no active treatment but the successful recruitment for the ProtecT prostate cancer study (comparing observation
with surgery or radiotherapy) has shown that this is not necessarily the case given careful discussion and consenting. Involve patients, encourage them to travel to research centres, increase trial availability!

Despite European collaboration via SIOP, paediatric trials are an ever greater challenge (there are only 450 cases per annum in the UK and these comprise numerous types especially when divided by stage and age as is now being done in medulloblastoma). For example, the BIOMEDE trial in diffuse pontine glioma (DIPG) is biologically driven and requires a biopsy, something considered unnecessary in the past because of safety concerns and as radiology is specific.

Given the failure of single agent kinase inhibitors and the fact that there is no one dominant biomarker in glioma, new trials should use combination chemotherapy and, for speed, there should be re-purposing of existing drugs.

Whilst there were calls for “adaptive randomisation”, new paradigms re clinical trial design and a change in philosophy regarding the level of evidence deemed acceptable, however, no actual examples were provided. It is obvious that Global, and not just European, collaboration is required in future.

Molecular Characterisation

Speaker after speaker emphasised differing prognoses and response to treatment in genomic sub groups and the fact that molecular stratification is now vital on a large scale. (This came at a time when it was announced that Illumina has been chosen by Genomics England to map the genetic makeup of 100,000 NHS patients at a cost of £100m. The project is currently in its pilot phase and will be completed by the end of 2017, making the UK a leader in personalised medicine).

However, biomarker assay is currently time consuming and accuracy inadequate; for example, although 1p 19q co-deletion occurs in >60% of cases of oligodendroglioma, it is usually assessed by means of fluorescent in situ hybridization (FISH) which is not considered sufficiently specific and there are many different tests used to assay MGMT promoter methylation. A more practical approach was described in the Stephen Baker Memorial Lecture by Stefan Pfister from Heidelberg who described an economically and technically feasible method to apply array- and next-generation sequencing-based technologies to replace individual tests for biomarkers. As the tumour genome is often much simpler in children than in adults, and after remarkable pilot results, their Phase II study - INFORM (individualised therapy for relapsed malignancies in childhood) – covers all paediatric tumour types at relapse, identifies drug targets from tissue samples and then compares the effect of giving random chemotherapy in one arm versus individualised therapy in the other. 55 centres in Germany are taking part with 30 patients recruited from 10 centres to date and 20 fully sequenced. Sequencing can be done even from very small samples and is accomplished in about 2 weeks. In >50% a drug target has been identified. Will centres in the UK join this trial?

In the meantime, are we ready to do as was recommended and stop giving temozolamide to patients with unmethylated MGMT?

Proton Beam Therapy

UK cancer survival doesn’t compare well with Europe or the rest of the world due to delays in diagnosis and poor optimisation of therapy. However, the point was made that it is surgery and radiotherapy that cures cancer and that the Kings Fund have stated that access to drugs alone has limited impact despite the Cancer
Drugs Fund costing £200m per annum without any associated evaluation. Dr Crellin, the National Clinical Lead for the Proton Beam Therapy Service Development Programme admitted that radiotherapy provision in the UK had been very poor in the 80s-90s and that we are only just getting enough intensity modulated radiation therapy (IMRT).

Proton beam therapy is no more effective than traditional radiotherapy but prevents collateral damage and should reduce the frequency of second malignancies. If one includes the cost of treating the adverse effects of traditional therapy, the total cost is no greater.

Since 2008, in the absence of proton beam installations in the UK (although Germany, for example, has 13 and there are 3 in France), 470 cases (224 adults and 383 children) have been approved for foreign treatment in two centres in the USA and one in Switzerland at a budget of £10m. 135 were not approved (mostly adults). It only takes 5-6 days to approve a case although issues of ethical fit and geographic location have precluded some. NHS England want to enhance this foreign programme by widening the paediatric list (for example, medulloblastomas have not been included to date), ensuring better equity across the country, extending it to include the Teenage Young Adult (TYA) group and developing outcomes tracking. The overseas budget has to include financing for travel and expenses. Electronic imaging transfer has been a challenge because, as the USA is not covered by EU legislation regarding data transfer, email has been impossible (it was stressed that there needs to be very good collaboration between the surgeon and radiology.)

Once the Christie and UCH sites are up and running in 2018 (2 years behind schedule), the UK plan is to treat 1500 cases per annum (1% of cancer patients; 900 rarer cancers and 600 difficult cases in common cancers).

Although one would not normally consider proton therapy for GBM, there is a trial of IMPT (proton beam) versus (IMRT) in progress at the MD Anderson Cancer Centre in Texas testing the hypothesis of less cognitive deficit.

Whilst ependymoma is one of the main indications for proton beam therapy, it requires an initial total resection. This is only occurring in 50-55% of children with ependymoma in the UK (mainly due tumour location) and the UK is poor in this respect, as is Germany, by comparison with France, Italy and the main US centre, St. Jude Children's Research Hospital, Memphis. Intra-operative MRI is considered essential for children in order to avoid having to take them back into theatre next day although “second look” surgery is justified by the significantly better survival gains. However, the more aggressive surgery in the USA is known to result in a higher degree of deficit, albeit abating over 5 years in many children. The question as raised whether we, too, should concentrate surgery in a smaller number of specialist centres in the UK as most surgeons only see a single case per year? As an alternative, the SIOP Ependymoma II trial will include a central national panel who will review each case.

Metastases

There were a number of both clinical and scientific papers devoted to the topic of CNS metastases. With approximately 25% of all cancer patients subsequently developing metastases there are about 30,000 per annum in the UK, of whom about 2000 are considered suitable for treatment. Incidence varies even within one primary tumour type and prognostic factors vary by type of primary.

Blanket application of palliative whole brain radiotherapy (WBRT) is no longer tenable in patients with multiple metastases. Observation and close monitoring with MRI (instead of adjuvant WBRT) is not detrimental for survival, QOL or cost. The ongoing HIPPO study will evaluate the effect of WBRT with hippocampal sparing on neurocognitive function.
Some degree of improvement in disease control in the brain has not translated as improved survival showing that spread of the disease to the brain is not the principal determinant of life expectancy in patients with disseminated disease. However there has been modest survival gain after local treatment (surgery, stereotactic radiosurgery (SRS)) with solitary metastases where active disease is largely confined to the brain and hence randomised clinical trials are required in patients where metastases are likely to be the determinant i.e. where systemic disease is controlled.

Trials should compare primary chemotherapy - response in the brain should reflect that of the systemic disease - with radiotherapy. Optimal timing in the course of the primary disease remains unknown as it is no longer certain that spread to the brain occurs late in the course of the disease. It is now thought more likely that small molecule chemotherapy needs to prevent metastases from forming much earlier.

Even though there are large numbers of patients with metastases, trials are again proving difficult to design; it is difficult to identify endpoints which have direct patient benefit and can demonstrate proof of principle in a situation confounded by systemic disease. In future we should test the experimental agent versus placebo - not as an add-on to current therapy – and must cease doing large unselected trials in favour of biomarker-enriched populations which are sub group specific.

**Tissue Bank**

BRAIN UK is a virtual brain bank incorporating tissue samples held in neuropathology departments throughout the UK. This has been extended to incorporate samples of particular relevance to research into brain tumours: the BRAIN UK Virtual Brain Tumour Archive. There are 450,000 archived cases (including non brain tumour diagnoses e.g. epilepsy) which can be made available for research purposes.

A major issue in collecting tissue is the differing patient pathways in various neuro-surgery centres. Additional factors are: patients don’t realise that tissue can be used, professionals are uncertain as to the best time to ask, not all surgeons are enthusiastic, there is variation regarding allocated resources and a lack of understanding as to how to set up a data bank.

The objective is that at least 80% of patients will be approached and at least 50% of consented samples will be banked. So far 24 out of a potential 29 centres are participating. It is anticipated that there will be 18,500 cases per annum in future.

**Fluorescence-Guided Resection and Local Chemotherapy**

Use of 5-ALA (Gliolan) to aid resection costs £1241 more per patient than white light microscopy, largely because patients survive longer and hence receive more chemotherapy. The cost per quality-adjusted life year (QALY) is £7424 which is well below the NICE threshold. Although it was pointed out that a special microscope, at a cost of approx £30k, is also needed, it was felt that this could usually be funded charitably.

It is vital to increase time to progression because overall survival comprises progression free survival (PFS) and post progression survival (PPS) where the later is generally about 6 months and from which the patient never re-enters stable disease. 80% of recurrence is within 2 cm of the resection. Hence, as the GALA-5 trial showed that 5-ALA and Carmustine wafers (Gliadel) did not compromise the Stupp regime, it is thought that there is a case for a trial of Stupp plus 5-ALA guided resection (IMPACT-GB). Once again, the choice of endpoint is problematic as PFS is not acceptable and it will require 1800 patients to use median survival (compared with 72 from 8 centres in GALA-5). It has been decided to utilise instead 2 year survival which will require a patient recruitment of 350 patients. If 20 centres each recruit one patient per month for 2 years this would equate to
480 patients; letters of support from every centre that has expressed an interest are now required (by Oct 2014). A central fund is available to support trial set up and running costs.

Another approach to local delivery is being studied in Nottingham. Young Investigator of the Year, Ruman Rahman, described the application of chemotherapy inside the resection cavity by means of a toothpaste-like mixture which maintains contact with the cavity wall. The paste sets at body temperature and the drug is released over time eg. temozolamide is released over 10 days.

Naturally, there was also much more but my next report will have to await BNOS 2015 on 1-3 July in Nottingham!

Maryanne Roach
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