

NCRI Brain Tumour Clinical Studies Group

Introduction

During the last year the Brain Tumour Clinical Studies Group (BTCSG) has made significant efforts to improve access to clinical studies for brain tumour patients in the UK. This is in the context of a rapid increase in the number of new agents that are being put forward as potentially useful drugs in treating these patient groups and increasing interest in the use of biomarkers to support treatment decisions. The Group had its second 3 year Progress Review in December 2008. The strengths of the Group and the issues it needs to address identified at the review can be found in Appendix 2. Following the review we have also focused efforts on addressing some of the long term issues that have limited activity in the past. During the last year the Group has brought forward new study ideas and developed protocols within the Group, which have attracted new funding. We have also continued working with other national and international study groups, and will activate a number of new collaborative studies in the coming year.

Membership and structure

We have continued to actively recruit new group members in relevant specialties during the past year. It has been encouraging that we have had significant interest from across the neuro-oncology field at each membership round. In particular we have been pleased to expand the surgical and medical oncology expertise within the Group. The subgroup structure that was set up following the interim review of group activity in 2007 has continued to expand and to provide an important mechanism for new study development. All the originally planned subgroups are now fully active with the exception of a Radiotherapy Technologies Subgroup, which has been subsumed into the broader NCRI Radiotherapy and Radiobiology initiative, the Clinical and Translational Radiotherapy and Radiobiology Working Group (CTRRWG).

Portfolio and accrual

There are 2 trials currently open in the Group's portfolio; 3 are in set up (see Table 1 and 2 below) and a further 6 are in development (Table 3). 2 further trials are open in collaboration with the CTRRWG and Lung CSG, OSCAR and TACTIC respectively. Although accrual has been poor in the last year this is essentially a reflection of a lack of available studies, which will be remedied in the next 6 months.

In the past year the Group has reported initial data from the BR12 trial, which compared the efficacy of Temozolomide against PCV (Procarbazine, CCNU, Vincristine) chemotherapy in chemo-naïve patients with recurrent malignant glioma. This provided very valuable data on comparative efficacy and toxicity between these regimes and, importantly also provided data on the effect of alternative scheduling of Temozolomide, which may inform future study design. The translational study linked to the BR12 trial is ongoing and preliminary data will be presented shortly.

The Group also collaborated with the EORTC on a randomised trial examining the role of whole brain radiotherapy after resection or radio-surgery for patients with 1-3 brain metastases. The trial was closed in October 2007 and preliminary data presented earlier this year. This has turned out to be a very valuable study, demonstrating that many patients with small numbers of brain metastases may be best treated by aggressive local therapy without whole brain radiotherapy. This is a very important message in the context of evolving management of good prognosis patients with controlled systemic disease.

A further phase III EORTC study addressing the effect of dose dense temozolomide compared to standard dose temozolomide in newly diagnosed glioblastoma multiforme patients opened in selected centres in the UK and recruited extremely rapidly, with several UK centres contributing large patient numbers. This trial closed to recruitment in June 2008. It was unfortunate that several UK centres who wished to activate the study failed to do so in time to be able to take part. We very much support moves to address some of the issues impacting on slow activation of EORTC studies in the UK.

The Group has collaborated with the EORTC in the development and implementation of a low-grade glioma trial, which compares Temozolomide versus radiotherapy in patients with progressive grade II astrocytomas, oligodendrogliomas and mixed tumours (EORTC 22033 – 26033, BR13). This trial is recruiting very well in other European countries and several centres are now open in the UK.

The major trials in set up include the CATNON (BR14/TATA trial) to examine the role of chemotherapy in patients with grade III astrocytoma (non1p,19q deleted anaplastic glioma). This study will be a major collaborative study between MRC/EORTC and RTOG with a substantial translational component. In addition a major EORTC study addressing use of chemotherapy in oligodendroglial tumours is in development and will be added to the portfolio. The ongoing study addressing use of high dose radiotherapy in high risk meningioma is currently waiting final agreement for adoption,

The Novel Agents Subgroup has also been successful in developing a study using PARP inhibitors in high grade glioma. This was approved for funding through CRUK's New Agents Committee (NAC) in April 09 and includes a significant translational component. This will open in 4-5 selected centres in late 2009.

Table 1: Brain Tumour CSG portfolio

Acronym	Title	PI(s)	Status
BR11	Adjuvant procarbazine, CCNU and vincristine chemotherapy in patients with highly anaplastic oligodendroglioma (in collaboration with the EORTC).	Professor Michael Brada	Closed
BR12	Temozolomide vs PCV chemotherapy in the treatment of recurrent malignant glioma	Professor Michael Brada	Closed
EORTC 22033-26033 - Low grade glioma trial (BR13)	Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas with stratification for genetic 1p loss: a phase III study	Dr Jeremy Rees	Open
EORTC 22952	No Radiotherapy versus Whole Brain Radiotherapy for 1 to 3 Brain Metastases from Solid Tumor after Surgical Resection or Radiosurgery. A Randomized Phase III Trial.	Dr R Soffietti	Closed
EORTC 26052	Phase III Trial comparing Conventional Adjuvant Temozolomide with Dose Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma	Dr Sara Erridge	Closed
Neo-adjuvant Carboplatin	Multicentre, Phase II Study of Carboplatin pre-irradiation in patients with primary glioblastoma	Professor Michael Brada	Closed

Trial	multiforme following biopsy		
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515 patients were recruited to Brain studies in 2008-9 representing 5.1% of incidence cases. Publications for the reporting year can be found in Appendix 1.

Trials in development

The table below summarises studies in set up or in development.

Table 2: Studies in set up

Title/patient group	Status	Subgroup/lead
Phase I study of PARPi AZD 2281 in GBM	Funding agreed NAC April 09.	Dr A Chalmers Novel Agents Sub-roup Professor P Collins Translational Subgroup
CATNON (BR14) Concomitant/adjvant TMZ with RT in grade III astrocytoma	Protocol finalized Awaiting MREC	Professor M Brada/Dr S Erridge
EORTC 26081 RT vs RT + TMZ in oligodendroglioma or mixed tumours	Protocol to be finalised	Professor R Rampling/Dr S Short
EORTC 22042 Adjuvant post operative high dose radiotherapy in atypical meningioma	Adoption agreed April 09	Selected centres local agreement
Brain tumour genetics study	Adopted 2008 Awaiting local agreements for activation	Professor R Houlston/Dr S Short

Table 3: Studies under development

Study	Design/status	PI
Radiotherapy with Adjuvant Chemotherapy for Adults with Intracranial Primitive Neuro-ectodermal Tumour (PNET) (CAPNET)	Single arm phase II Submission to NIHR planned	Professor Roger Taylor
Phase II study of schwannoma	Phase II Under development in new agents group	Professor O Hanneman
Radio-surgery and Avastin for brain metastases from solid tumours	Randomised phase II Under discussion with	Dr Paul Mulholland

	Roche/GammaKnife	
Quality of life issues in carers of brain tumour patients	Pilot questionnaire study Palliative Care Subgroup	Dr Angela Costello
Use of complementary medicines by brain tumour patients	Questionnaire study Pilot phase ongoing	Dr Sosie Kassab

Meetings

A major focus in the last year has also been forging closer links with other relevant groups including young adult and paediatric oncology groups. A second one day meeting was held in December 2008 to discuss and plan a future joint agenda focusing on use of novel agents. Following the initial meeting in late 2007 an editorial has been published jointly in Clinical Oncology.

Collaborations

The Group is collaborating in two national brain metastases trials. The OSCAR trial, developed with the Radiotherapy CSG is assessing the role of radiotherapy in poor prognosis patients with multiple brain metastases from non-small cell lung cancer and will randomise patients between best supportive care and whole brain irradiation. The TACTIC trial, developed in collaboration with the Lung CSG, is assessing the value of Erlotinib (Tarceva) in addition to whole brain radiotherapy using a randomised phase II trial design in patients with inoperable brain metastases from non-small cell lung cancer. Both trials are now open. Further studies for patients with brain metastases are under discussion with the relevant NCRI Clinical Study Groups.

Other activities

The Group has been aware of the problems inherent in clinical research in rare tumour types in accessing local resources to support study entry including data management, research nurse and research administration support. Following discussions at CSG meetings an initiative has been agreed with CRUK and The Samantha Dickson Brain Tumour Trust (SDBTT) to make targeted funding available for clinical research into brain tumours through the Comprehensive Biomedical Centres. SDBTT agreed to fund a project officer post at 0.2FTE for the group in 2007. We have been unable to attract interest in this post and therefore requested increased funding, which was agreed through CRUK. We hope to appoint to a 0.4FTE post at UCL shortly.

The Group has been made aware of problems specific to the UK that make participation in European studies challenging, including long lag time between MREC agreement and local set up and variability in local sponsorship agreements. We hope to address these in collaboration with the NCRI EORTC Liaison Officer.

In the coming year there will be a unique opportunity to access support for brain tumour studies through the SDBTT/CRUK joint initiative, which will provide funds for phase II studies in this area. The relevant subgroups, in particular the Novel Agents Subgroup have been working towards applications for this funding stream.

3-year strategy

The BTCSG's three year strategy is to:

- Increase proportion of brain tumour patients in UK that are included in high quality clinical studies

- Continue to work closely with the international research community to involve UK patients in available studies
- Introduce novel surgical and radio-therapeutic technologies within well defined studies in good performance status high grade glioma patients
- Define standard treatment protocols for patients with rare tumours in context of clinical studies in which biological end points can be measured
- Identify issues in brain tumour patient carer groups and the means to address these
- Develop systems for UK wide imaging based monitoring of response to treatment

Priorities for next year

The Group's priorities for next year are to:

- Expand of portfolio focusing on phase II studies, utilizing new funding streams
- Contribute to an initiative to set up a brain tumour registry for the UK
- Appoint a project officer post to support new initiatives
- Significantly increase recruitment to phase III studies through the EORTC collaborative studies now available
- Work with NAC to set up the early phase study using a PARP inhibitor

Dr Susan Short, Chair

Appendix 1

Key strengths and issues from the Progress Review December 2008

The Brain CSG had its first 3 year review June 2005, an interim review in February 2007 and its second three year review on 11th December 2008.

Strengths:

- The momentum developed and progress made since the interim review
- Strong leadership which has brought the Group together and re-energised it
- Appropriate subgroup structure
- Clear and appropriate subgroup strategies and overall Group's strategy
- Attempts to improve links with the EORTC
- Increased and broadened membership

The Group needs to consider:

- Developing a critical mass of studies
- Ways to substantially increase accrual
- Improving links with the EORTC
- Increasing the number of champions in the Group for the EORTC linkage to enable rapid progress to be made
- Building up the phase II portfolio through the Novel Agents Subgroup working with NCRN-AZ initiative, Samantha Dickson Trust and ECMCs
- Taking forward their plans for metastatic disease
- Identifying subgroup chairs for those subgroups currently chaired by the CSG Chair
- Identifying additional medical oncologists and consumer representatives for the subgroups
- Appointing to the Project Officer post
- Identify small scale trials which can act as pilots for larger studies
- How the various tissue banks can be co-ordinated
- Holding a strategy away day/residential possibly with BNOS

The Panel agreed that the NCRN needed to:

- Explore how network resources can be galvanised to support rare tumours
- Explore sources of funding for attendance of the Chair or designees at international conferences of relevance to the portfolio of the Group

Appendix 2

2008/09 Publications and abstracts

Biswas S, Burke A, Cherian S, Williams D, Nicholson J, Horan G, Jefferies S, Williams M, Earl HM, Burnet NG, Hatcher H. Non-pineal supratentorial primitive neuro-ectodermal tumors (sPNET) in teenagers and young adults: Time to reconsider cisplatin based chemotherapy after cranio-spinal irradiation? *Pediatr Blood Cancer*. 2009 Feb 7. [Epub ahead of print]

Price SJ, Fryer TD, Cleij MC, Dean AF, Joseph J, Salvadore R, Wang DD, Hutchinson PJ, Clark JC, Burnet NG, Pickard JD, Aigbirhio FI, Gillard JH. Imaging regional variation of cellular proliferation in gliomas using 3'-deoxy-3'-[18F]fluorothymidine positron-emission tomography: an image-guided biopsy study. *Clin Radiol* 2009; 64(1): 52-63 [Epub 2008 Sept 4]

Burnet NG, Jena R, Jefferies SJ, Kirkby NF, Treasure FP. CNS oncology: heavy disease burden and low research spending necessitate imaginative approaches to clinical research. *Brit J Neurosurg* 2008; 22(3): 332-338

S C Short, Survival from brain tumours in England and Wales up to 2001 Clinical Commentary
Br J Cancer. 2008 Sep 23;99 Suppl 1:S102-3.

R Taylor, B Pizer, SC Short, Promoting collaboration between adult and paediatric clinical trial groups *Clinical Oncology*.2008 Nov 20;9. 714-716

Siow-Ming Lee, Michael Brada, Sally Stenning, Lindsay Thompson, Rhian Gabe for BR12 Collaborators. A randomised trial of procarbazine, CCNU and vincristine (PCV) VS temozolomide (5-day or 21-day schedule) for recurrent high grade glioma (MRC BR12, ISRCTN83176944). *Annals of Oncology* 19 (Supplement 8): viii1-viii4 abstract LBA5.

Michael Brada for the BR12 Collaborators. A randomised trial of procarbazine, CCNU and vincristine (PCV) vs temozolomide (5-day or 21-day schedule) for recurrent high grade glioma (MRC BR12, ISRCTN83176944).

Dungey FA, Löser DA, Chalmers AJ, Replication-dependent radiosensitisation of human glioma cells by inhibition of poly(ADP-ribose) polymerase: mechanisms and therapeutic potential. *Int J Radiat Oncol Biol Phys*. 2008;72(4): 1188-97.

Catt S, Chalmers A, Fallowfield L. Psychosocial and supportive-care needs in high-grade glioma. *Lancet Oncology* 2008; 9(9): 884-91.

