CONFERENCE SCENE

For reprint orders, please contact: reprints@futuremedicine.com

A selected review of abstracts from the 17th Annual Scientific Meeting of the Society for Neuro-Oncology

Marc C Chamberlain*

17th Annual Scientific Meeting of the Society for Neuro-Oncology, Washington, DC, USA, 15–18 November 2012

The Annual Scientific Meeting of the Society for Neuro-Oncology (SNO) is the largest neuro-oncology annual meeting in the USA and provides an exciting venue for the presentation of new brain cancer clinical trials and research data primarily pertaining to gliomas. The SNO 2012 meeting, comprising of one education day, three days of presentation, 80 oral presentations and 400 abstracts, provides a current overview of neuro-oncology including metastatic diseases of the CNS as well as primary brain tumors. This short article, highlights select abstracts presented at this meeting to provide a snapshot of a large and multifaceted meeting.

Metastatic disease of the CNS

■ Parenchymal brain metastases

A study by the Radiation Treatment Oncology Group (RTOG 0614) compared whole-brain irradiation (37.5 Gy in 15 fractions) with or without the *N*-methyl *D*-aspartate receptor antagonist memantine (20 mg/day) in patients (*n* = 508) with polymetastatic brain metastases [1]. Approximately 32% of patients completed the protocol with a 24-week assessment. Although the study was negative (the primary end point was memory decline at 24 weeks as measured by the Hopkins Verbal Learning Test – Revised Delayed Recall), a statistically nonsignificant trend was seen in improved cognition and recall at 24 weeks in patients treated with memantine.

Primary brain tumors

■ Gliomas

Low-grade gliomas

A study from Germany emphasized the importance of using biopsies directed at ¹⁸fluoroethyl-tyrosine PET imaging hotspots to determine tumor grade and outcome in what, by anatomic MRI, appear to be low-grade gliomas [2]. The study suggested that increased uptake of the amino acid radioligand predicted higher tumor grade and decreased survival. An Italian prospective Phase II trial of dose-dense temozolomide (ddTMZ) in patients with progressive oligodendroglioma demonstrated a partial response rate of 35%, a significant reduction (defined as >50% decrease from baseline) in seizures (85%)

News & Views

News

Journal Watch

Conference Scene

*Department of Neurology/Division of Neuro-Oncology, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 825 Eastlake Avenue E, PO Box 19023, MS G4940, Seattle, WA 98109–1023, USA; Tel.: +1 206 288 8280; Fax: +1 206 288 2000; chambmc@u.washington.edu

and a median progression-free survival (mPFS) of over 33 months [3]. Approximately 40% of patients stopped ddTMZ due to toxicity and changed to standard-dose temozolomide (sdTMZ). Whether these results differ significantly from sdTMZ is uncertain and perhaps warrants a prospective randomized trial, as suggested by the authors.

Anaplastic gliomas

Up-front trials

The long-term follow-up studies from the European Organization for the Research and Treatment of Cancer (EORTC 26951) and the RTOG 9402 trials for newly diagnosed anaplastic oligodendroglial tumors (AOTs) were presented again and demonstrated a significant survival advantage for the 1p19q codeleted cohort of AOTs treated with adjuvant radiotherapy (RT) and procarbazine, lomustine and vincristine (PCV) chemotherapy [4]. These studies are practice changing as both demonstrate a twofold increase in median overall survival in patients with 1p19q codeleted AOTs treated initially with RT and PCV compared with RT alone followed at recurrence with an alkylator-based chemotherapy (RTOG 14.7 vs 7.3 years and EORTC 12.8 vs 5.5 years). Additionally, there was no survival advantage seen in the larger group of patients with AOTs that are uni- or non-deleted when comparing RT and PCV to RT alone, suggesting a limited (if any) effect of adjuvant PCV on survival in patients with nondeleted anaplastic glioma (median overall survival ~2.5 years in either treatment arm). Both the EORTC and RTOG analyses suggest further molecular characterization of these morphologically similar tumors might identify tumor subtypes that respond differentially to treatment [5]. RTOG data suggests that in uni- or non-deleted AOTs, *IDH1* and G-allele (a single nucleotide polymorphism susceptibility marker) may identify tumors responsive to RT and PCV. Similarly, EORTC used gene expression profiling to identify six molecular subtypes, of which one subtype (IGS-9, characterized by 1p10q codeletion and *IDH1* mutation) particularly benefits from RT and PCV. These data strongly suggests that

molecular subtypes are identifiable within AOTs and also that they appear prognostic and may assist in refining therapy, for example, identifying chemosensitive subtypes. This question (benefit of adjuvant chemotherapy) is being further explored in an ongoing prospective Phase III EORTC trial (CATNON) comparing RT alone to RT and temozolomide (TMZ).

RTOG presented final data on the RTOG0131 trial that utilized ddTMZ as neoadjuvant therapy in patients with newly diagnosed AOTs. Out of 40 patients that entered the study, 37 were analyzed for 1p19q codeletion, of which 23 tumors were codeleted. mPFS and overall survival were similar to the RTOG 9402 codeleted cohort suggesting comparable activity of neoadjuvant ddTMZ followed by RT and TMZ to RT and PCV. The pragmatic question of whether RT and TMZ is as efficacious as RT and PCV will be adjudicated in a soon to open trial (CODEL) comparing these regimens in patients with newly diagnosed codeleted AOTs [JAECKLE K, PERS. COMM.].

In a further analysis of data from the German NOA-04 trial (RT vs TMZ or PCV chemotherapy for newly diagnosed anaplastic glioma), methylation of the tumor *MGMT* gene promoter and the presence of *IDH1* mutation was prognostic and associated with similar median overall survival irrespective of whether patients received RT or TMZ and/or PCV [6]. However, in patients with wild-type *IDH1* and methylated *MGMT*, a survival advantage was only seen in patients with receipt of TMZ and/or PCV.

Glioblastoma

Up-front trials

A preliminary report of the AVAglio trial comparing standard of care (SOC; RT and TMZ) with or without bevacizumab (BEV) indicated that one of the primary co-end points was met: that of mPFS [7]. Investigators determined that mPFS was 10.6 months in the BEV arm compared with 6.2 months in the SOC arm. Similarly, in the independent radiology facility assessment, mPFS was 8.4 months in the BEV arm and 4.3 months in the SOC arm. Median follow-up was only 14 months, however, 1-year survival was similar in

both treatment arms (66 vs 72%). Secondary end points included a health-related quality of life assessment, which showed longer improvement or stability from baseline in patients treated with BEV as well as longer maintenance of a Karnofsky performance status >60%. Patients on the BEV arm more often discontinued steroids and had delayed reinstitution of steroids with disease progression. Toxicity did not appear markedly increased in the BEV arm, however, the rate of discontinuance due to toxicity was twofold higher in the BEV arm (13.2 vs 24.6%). Maturation of the data assessing survival is anticipated next year. Similarly, Ranjan *et al.* re-presented long-term follow-up data on 125 newly diagnosed glioblastoma (GBM) that were treated with SOC and upfront BEV followed by post-RT TMZ and BEV [8]. mPFS and overall survival was 14 and 20.9 months, respectively. The German NOA-08 trial (elderly patients with GBM or anaplastic astrocytoma treated with standard dose RT [60 Gy] or ddTMZ) was re-presented demonstrating a survival advantage with ddTMZ treatment in elderly patients whose tumors had promoter methylation of the *MGMT* gene [9]. This trial and a similar Nordic trial (elderly GBM patients treated with standard or hypofractionated RT vs sdTMZ) suggest elderly patients with GBM show similar survival benefit when treated with TMZ only and deferred RT when compared with RT only. Survival is also improved in the small cohort (~30%) of elderly patients with GBM and *MGMT* methylated tumors when treated with TMZ, a practice changing treatment strategy.

A multi-institutional observational analysis of newly diagnosed GBM (n = 326) confirmed overall survival was improved in patients with *MGMT* promoter methylation who received RT and TMZ [10]. Complete resection was also found to be an independent prognostic variable whereas incomplete resection, similar to biopsy, did not significantly improve survival. Not stated, however, was a comparison between groups of patients with newly diagnosed GBM otherwise considered for complete resection that underwent partial versus complete resection.

A revised RTOG recursive portioning analysis model was presented that incorporated prior mRNA profiling, *MGMT* promoter methylation and *IDH1* mutation (the second RTOG recursive portioning analysis model termed the molecular clinical prognosticator model) with pAKT, c-met and *MGMT* protein determined by the Automated Quantitative Analysis platform, using a subset of patients from the RTOG 0525 clinical trial [11]. The current model accurately determined molecular subgroups of GBM and, if validated, may be promising for stratifying patients with respect to treatment.

Salvage trials

A retrospective study of BEV in recurrent GBM from University of California (CA, USA)/Kaiser Permanente Sunset (LA, USA) analyzed BEV use following failure of RT and TMZ in first, second and third or more recurrences [12]. The mPFS following initiation of BEV was similar in all three groups (117 days) as was survival following progression on BEV (98 days). These results suggest deferred use of BEV for latter recurrences is not associated with diminished efficacy.

RTOG reported on the Phase I component of a trial of the oral PARP inhibitor, veliparib, in conjunction with two doses of TMZ (sdTMZ and ddTMZ) in patients with recurrent GBM previously treated with RT and TMZ [13]. The trial, now open as a two-arm Phase II study, determined the safety of using veliparib (40 mg orally two-times a day) in conjunction with ddTMZ (21 out of 28 day schedule of 75 mg/m² per day). PARP inhibitors impair base excision repair, a DNA damage system that repairs over 80% of all DNA adducts generated by alkylating chemotherapy and may represent a rationale for enhancing TMZ tumor cytotoxicity.

Quality of life

Three studies evaluated quality of life in either caregivers of patients with gliomas or cognitive outcome in long-term survivors of high-grade gliomas [14–16]. In the study of quality of life in caregivers of patients with primary brain tumors, a randomized

trial comparing caregiver psychological support versus none, caregivers in the active intervention arm appeared to benefit, suggesting an unrecognized need in these at-home healthcare providers [14]. Two studies of long-term survivors of high-grade gliomas (defined as either 3- or 5-year survival post-diagnosis), came to similar conclusions [15,16]. One study reported high rates of fatigue and depression as well as cognitive impairment in the majority (69%, 46% of which had mild impairment) [15]. The complimentary study showed that, notwithstanding high performance status and radiologic disease stability, the majority of patients were in the lowest quartile

for cognitive function across all domains, including executive function, processing speed, reaction time and memory [16].

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Wefel JS, Shook S, Brown PD *et al.* Memantine for the prevention of cognitive dysfunction in patients receiving whole brain radiotherapy (WBRT): first report of RTOG 0614, a placebo-controlled, double-blinded, randomized trial. *Neuro. Oncol.* 14(Suppl. 6), Abstract NC-08 (2012).
- Kunz M, Armbruster L, Jansen N *et al.* Hot-spots in dynamic ¹⁸FET-PET are associated with unfavorable outcome in patients with suspected WHO grade II glioma. *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-20 (2012).
- Rudà R, Bertero L, Bosa C *et al.* Dose-dense temozolomide as initial treatment for progressive low-grade oligodendroglial tumors: a Phase II study of the Italian Association of Neuro-Oncology. *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-33 (2012).
- van den Bent MJ, Brandes AA, Taphoorn MJ *et al.* Long-term follow-up of EORTC 26951, a randomized trial on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors: a report of the EORTC BTG. *Neuro. Oncol.* 14(Suppl. 6), Abstract MR-03 (2012).
- French P, Erdem L, Gravendeel M *et al.* Intrinsic molecular subtypes of glioma are prognostic and predict benefit from adjuvant PCV chemotherapy in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. *Neuro. Oncol.* 14(Suppl. 6), Abstract OM-21 (2012).
- Wick W, Meisner C, Hentschel B *et al.* Prognostic or predictive value of O⁶-methylguanylmethyltransferase promoter methylation in malignant gliomas depends on isocitrate dehydrogenase 1 mutations. *Neuro. Oncol.* 14(Suppl. 6), Abstract OM-23 (2012).
- Chinot O, Wick W, Mason W *et al.* Phase III trial of bevacizumab added to standard radiotherapy and temozolomide for newly diagnosed glioblastoma: mature progression-free survival and preliminary overall survival results in AVAglia. *Neuro. Oncol.* 14(Suppl. 6), Abstract OT-03 (2012).
- Ranjan T, Desjardins A, Peters KB *et al.* Long-term follow-up of a Phase II trial of upfront bevacizumab with temozolomide and radiation therapy followed by bevacizumab temozolomide, and irinotecan for newly diagnose glioblastoma multiforme (GBM). *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-83 (2012).
- Weller M, Meisner C, Platten M *et al.* MGMT promoter methylation predicts benefit from temozolomide *versus* radiotherapy in malignant astrocytomas in the elderly: the NOA-08 trial. *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-06 (2012).
- Kreth F-W, Thon K, Simon M *et al.* Complete, but not partial resection is important in the era of radiotherapy, concomitant and adjuvant temozolomide for glioblastoma patients. *Neuro. Oncol.* 14(Suppl. 6), Abstract NS-13 (2012).
- Charkravarti A, Wang M, Aldape K *et al.* A revised recursive partitioning analysis model for glioblastoma based upon multi-platform biomarker profiles. *Neuro. Oncol.* 14(Suppl. 6), Abstract MR-02 (2012).
- Selfridge J, Piccioni DE, Zurayk M *et al.* Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy. *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-97 (2012).
- Robins HI, Wang M, Gilbert MR *et al.* Phase I results from RTOG 0929, a randomized Phase I/II study of ABT-888 (Veliparib) in combination with temozolomide (TMZ) in recurrent TMZ-resistant glioblastoma. *Neuro. Oncol.* 14(Suppl. 6), Abstract NO-14 (2012).
- Boele F, Hoeben W, Hilverda K *et al.* Augmenting quality of life and mastery of informal caregivers of high-grade glioma patients: a randomized controlled trial. *Neuro. Oncol.* 14(Suppl. 6), Abstract SM-27 (2012).
- Amidei CM, Lovely M, Page MD *et al.* Symptoms in adult long-term survivors of malignant brain tumors. *Neuro. Oncol.* 14(Suppl. 6), Abstract SM-19 (2012).
- Peters KB, Woodring S, Herndon JE *et al.* Long-term survivorship in primary glioblastoma: a focus on neurocognition. *Neuro. Oncol.* 14(Suppl. 6), Abstract NC-07 (2012).