A selected review of abstracts from the 4th Quadrennial Meeting of the World Federation of Neuro-oncology

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The 4th Quadrennial Meeting of the World Federation of Neuro-Oncology (WFNO), San Francisco, CA, USA, 21–24 November 2013

The 4th Quadrennial Meeting of the World Federation of Neuro-Oncology (WFNO) was the largest neuro-oncology meeting that meets once every 4 years and brings together clinicians and scientists from all parts of the world whose focus is on new brain cancer clinical trials and research primarily pertaining to gliomas. The WFNO 2013 meeting included 1 education day, 2.5 days of presentation, 13 sunrise sessions, one town hall meeting, one mini-symposium, 130 oral presentations and 900 abstracts. This short meeting review highlights select adult clinical abstracts presented at WFNO 2013 that will only in part encompass the contents of a large and multifaceted meeting.

Metastatic disease of the CNS

• Parenchymal brain metastases

A single-arm Phase II study by the Radiation Treatment Oncology Group (RTOG 0933) presented by Gondi (University of Wisconsin, WI, USA) evaluated whole-brain irradiation (WBI; 30 Gy in ten fractions) and conformal avoidance of the hippocampus in patients ($n = 113$) with polymetastatic brain metastases (BM) [1]. The primary end point was the Hopkins Verbal Learning Test-Revised Delayed Recall at 4 months. Preclinical data suggest that hippocampal radiation dose may contribute to cognitive neurotoxicity. In addition, several clinical studies suggest that memory assessment by the Hopkins Verbal Learning Test-Revised Delayed Recall is a robust tool for assessing radiation-induced cognitive injury. Using a historical control from a previous Phase III trial that used a similar instrument to assess cognition, the trial suggests WBI with hippocampal avoidance diminishes memory dysfunction without sacrificing efficacy regarding control of BM. Based on the results of this study, RTOG is planning a Phase III trial to test this hypothesis. Gore (Royal Marsden Hospital NHS Trust, London, UK) presented results from an expanded access trial for patients ($n = 338$) with renal cell carcinoma (RCC) complicated by BM in whom treatment entailed WBI and sunitinib given either continuously (37.5 mg/day) or by an intermittent schedule [2]. Treatment was well tolerated as observed side effects were not dissimilar to those seen in patients with RCC without BM treated with sunitinib. The authors suggest that for patients with RCC and BM in whom there are limited treatment options, the combination of sunitinib and WBI is safe, and with encouraging efficacious.

KEYWORDS

- primary and secondary (metastatic) brain tumors
- WFNO/SNO 2013 clinical abstracts

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• Leptomeningeal metastases

Patel (Penn State Hershey Medical Center, PA, USA) reported on the diagnostic utility of cerebrospinal fluid (CSF) multiparameter flow cytometry using the CellSearch® (Janssen Diagnostics, NJ, USA) instrument to enumerate malignant cells in CSF in 13 patients with breast cancer and carcinomatous meningitis [3]. The results of CellSearch enumeration of tumor cells was compared with the standard diagnostic triad of CSF cytology, neuraxis MRI and neurological examination. The authors conclude that CellSearch was more sensitive, specific and cost effective. Bromberg (Erasmus MC Daniel der Hoed Cancer Center, Rotterdam, The Netherlands) assessed intra-CSF rituximab in 33 patients with lymphomatous meningitis [4]. Rituximab was administered twice-weekly by intralumbar administration. Dosing initially at 25 mg/dose resulted in a transient painful radiculopathy that required a dose reduction to 10 mg/dose and without apparent toxicity. One hour post-rituximab median CSF levels were 120 µM/ml following a 10-mg dose, higher levels than seen in the serum after intravenous administration of rituximab. Of 18 patients with positive CSF cytology, eight failed to clear with intra-CSF rituximab. The authors conclude that the maximum tolerated dose for intralumbar rituximab is 10 mg administered twice-weekly and is associated with little toxicity, and appeared efficacious.

Primary brain tumors

• Gliomas

Low-grade gliomas

A mini-symposium was dedicated to low-grade gliomas (LGG), at which the faculty discussed current thinking and management. Berger (University of California, USA) discussed surgical approaches to LGG, including the survival benefit afforded to patients with LGG in whom an image-verified complete resection is obtained, the value of awake craniotomy with intraoperative mapping for tumors in the eloquent brain, the need for second completion surgeries so as to achieve an image-verified complete resection and the hypothesis that complete resection mitigates transformation at recurrence to a higher-grade glioma [5]. Brown (University of Texas MD Anderson Cancer Center, TX, USA) revisited the RTOG 9802 trial that compared radiotherapy (RT) with RT + PCV (procarbazine, lomustine [CCNU] and

vincristine) chemotherapy in high-risk LGG and suggested, based on historical comparisons, a potential benefit to combination therapy in this subset of LGG, with the caveat that the outcome data remain immature [6]. This hypothesis is being formally evaluated in a currently open and accruing intergroup prospective randomized trial (Eastern Cooperative Oncology Group/RTOG/Alliance). Baumert presented results from the European Organization for Research and Treatment of Cancer (EORTC 22033) that compared dose-dense temozolomide (TMZ) with RT in patients with progressive LGG [7]. The primary end point was progression-free survival (PFS). The study failed to meet the prespecified end point that of TMZ being superior to RT with respect to PFS (40 vs 47 months, respectively). In addition, although both 1p19q codeletion and O⁶-methylguanine DNA methyltransferase (MGMT) promoter methylation were prognostic, neither were predictive of response to therapy. Soffietti assessed the role of alkylator chemotherapy in the treatment of LGG and presented data showing a benefit with respect to medically refractory seizures, a common clinical scenario in patients with LGG and epilepsy [8]. Aldape (University of Texas MD Anderson Cancer Center) presented data that suggest a combination of histology and molecular biomarkers was most informative with respect to classifying and prognosticating LGG [9]. In particular, the utility of the *IDH1* mutational status, presence or absence of the 1p19q codeletion and proliferative index best categorized LGG. Haas-Kogan (University of California) presented data indicating that the oncogene mTOR was a valid target in LGG and showed early promising results with the oral-targeted agent everolimus in recurrent LGG [10]. Yen (Agiros Pharmaceutical, MA, USA), along a similar theme, suggested that the *IDH1* mutation was a valid target in LGG and showed early preclinical data with the *IDH1* inhibitor AGI-5198 (Agiros Pharmaceuticals) that delays growth and promotes differentiation of glioma cells *in vitro* [11].

Two quality of life (QoL) assessments in LGG were presented. The first was by Fisher (University of Western Ontario, Canada) regarding the RTOG 0424 clinical trial using RT + TMZ in high-risk patients, which reported a better than historical control 3-year overall survival of 73% and with, importantly, maintenance of QoL, as well as

neurocognitive function in survivors (MR-009) [12]. The second QoL report by Reijneveld (VU University Medical Center, Amsterdam, The Netherlands) suggested no clear differences between assessments in the EORTC 22033 study mentioned above comparing TMZ with RT, with the primary end point of PFS (LB-004) [13].

Anaplastic gliomas

Upfront trials

Omuro (Memorial Sloan–Kettering Cancer Center, NY, USA) presented data from a Phase II study in patients ($n = 41$) with anaplastic oligodendroglioma (32 manifesting 1p19q codeletion) that utilized TMZ for six cycles and in stable or radiographically responding patients ($n = 20$), then proceeded to autologous peripheral stem cell transplantation with high-dose chemotherapy (thiotepa and busulfan) and deferred RT (NO-108) [14]. Two-year survival data suggest that this regimen is similar to the RT + PCV treatment platform and spares patients the potential radiation-associated neurotoxicity. Whether autologous peripheral stem cell transplantation is a practical alternative to the current standard-of-care (SOC) RT + PCV seems unlikely to be addressed in a prospective clinical trial.

van den Bent (Erasmus MC Daniel der Hoed Cancer Center) reanalyzed the EORTC 26951 study of RT versus RT + PCV for anaplastic oligodendroglial tumors (AOT), with particular interest in determining whether there is a subgroup of uni- or non-1p19q-deleted AOT that respond to adjuvant PCV chemotherapy [15]. Survival of the upper quartile of such patients appears to suggest a benefit to treatment with RT + PCV. Reanalysis suggests that 1p19q uni- or non-deleted tumors that are *MGMT* promoter methylated, as determined by the Illumina platform (Illumina Inc., CA, USA) and that evaluates multiple CpG sites, may represent a subgroup of patients with noncodeleted AOT that is responsive to adjuvant PCV chemotherapy. The presence of a hypermethylated phenotype; that is, glioma-CpG island methylation phenotype-positive, was of borderline prognostic significance. This hypothesis probably will be explored in the currently open prospective randomized trial, CATNON, for noncodeleted anaplastic gliomas comparing RT with various iterations of concurrent and adjuvant TMZ.

Glioblastoma

Upfront trials

Five major adjuvant trials of newly diagnosed glioblastoma (GBM) were presented, four of which had previously been presented in other meetings. Chinot (Aix-Marseille University, Marseille, France) discussed the final results from AVAglio, suggesting that one of two primary end points were met; that is, a prespecified improvement in PFS [16]. However, the overall response (OS) was not different when comparing SOC with the experimental arm, SOC plus bevacizumab. In addition, Taphoorn indicated that QoL was significantly improved in patients treated with bevacizumab, as was maintenance of performance status, and steroid requirement was diminished [17]. By contrast, Gilbert (UT MD Anderson Cancer Center) reviewed final outcome results for RTOG 0825, a study similar in design to AVAglio, which did not meet either primary study coendpoints; that is, improvement in PFS or OS [18]. In addition, Armstrong (UT MD Anderson Cancer Center) [19] and Wefel (UT MD Anderson Cancer Center) [20] showed no improvement in QoL, neurocognitive function or symptom burden in patients treated with bevacizumab compared with SOC. These conflicting data are difficult to reconcile; however, notably, there were fundamental differences in how the analysis was performed, particularly with respect to QoL. Furthermore, the statistical modeling of the primary end points in RTOG 0825 have clearly been outlined as compared with AVAglio, where the relative statistical weighting of PFS and OS is unclear. It seems unlikely that the two trial data sets will be merged and reanalyzed by a third party so as to resolve the observed discrepancies. Nonetheless, as OS was not improved in either trial, it would appear that bevacizumab as a treatment option for newly diagnosed GBM in conjunction with SOC has a low likelihood of regulatory approval for this indication. Whether these trials influence regulatory approval of bevacizumab for recurrent GBM is uncertain.

Two other notable trials were presented, the GLARIUS trial by Herrlinger (University of Bonn, Germany) [21] and the CORE trial by Nabors (University of Alabama, USA) [22]. GLARIUS was a trial comparing SOC with RT + bevacizumab followed post-RT by bevacizumab + irinotecan in nonmethylated *MGMT* newly diagnosed GBM. The trial showed an improved PFS in the bevacizumab arm not

dissimilar to AVAglio [16] and RTOG 0825 [18]. The CORE trial compared SOC with or without the integrin inhibitor cilengitide in unmethylated MGMT newly diagnosed GBM and showed no statistical improvement in PFS or OS. These results, which mirror the CENTRIC trial [23] in newly diagnosed MGMT methylated GBM utilizing the same agent, probably suggest no further development of cilengitide in GBM.

Salvage trials

Taal (Erasmus MC Daniel der Hoed Cancer Center) reported on the Dutch BELOB trial that compared bevacizumab with CCNU with the combination in patients with recurrent GBM [24]. As noted previously, 6-month PFS was best with the combination of bevacizumab + CCNU, suggesting a possible chemosynergy effect not previously defined in neuro-oncology with bevacizumab. This synergistic effect, if real, is being evaluated in a larger randomized Phase III trial by EORTC (EORTC 26101 [25]).

• Primary CNS lymphoma

Omuro presented the first randomized multicentric chemotherapy-only Phase II trial in elderly patients (defined as age >60 years) with primary CNS lymphoma comparing high-dose methotrexate + TMZ with high-dose methotrexate, procarbazine, vincristine and high-dose cytarabine [26]. All outcome measures (survival and QoL) favored the methotrexate, procarbazine, vincristine and high-dose cytarabine treatment arm, suggesting a possible new standard treatment for primary CNS lymphoma in the elderly.

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References

- Gondi V, Mehta M, Pugh S *et al.* Memory preservation with conformal avoidance of the hippocampus during whole brain radiotherapy (WBRT) for patients with brain metastases: preliminary results of RTOG 0933. *Neuro Oncol.* 15(Suppl. 3), iii94–iii95, Abstract NC-012 (2013).
- Gore M, Hariharan S, Porta C *et al.* Sunitinib in patients with brain metastases from metastatic renal cell carcinoma (mRCC) – final results from a global expanded access trial. *Neuro Oncol.* 15(Suppl. 3), iii110, Abstract NO-049 (2013).
- Patel A, Allen J, Dicker D *et al.* Making neoplastic meningitis diagnosable – a simple versatile powerful alternative to conventional techniques. *Neuro Oncol.* 15(Suppl. 3), iii126, Abstract NO-112 (2013).
- Bromberg J, Schouten H, Schaafsma R *et al.* Rituximab concentration and effect after intrathecal administration of rituximab in CNS relapse of systemic lymphoma – results from a prospective Phase II HOVON 80 study. *Neuro Oncol.* 15(Suppl. 3), iii102, Abstract NO-018 (2013).
- Berger MS. Evidence for the importance for extent of resection. Minisymposium on low grade gliomas: facts, controversies and future challenges. Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Brown P. Initial results of RTOG 9802; will this be EORTC26951/RTOG 9402 redux? Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Baumert B. The international EORTC/NCIC-CTG/TROG/MRC-CTU low grade trial: temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) LGG. *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Soffietti R. Chemotherapy as initial treatment: response, monitoring and new studies. Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Aldape K. Beyond histopathology; molecular classification. Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Haas-Kogan D. Targeting m-TOR. Aberrant signaling pathways and clinical trials for low grade glioma. Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Yen KL. Targeting *IDH1* mutations. Aberrant signaling pathways and clinical trials for low grade glioma. Presented at: *4th Quadrennial Meeting of the World Federation of Neuro-Oncology*. San Francisco, CA, USA, 21–24 November 2013.
- Fisher B, Chen H, Macdonald D *et al.* RTOG0424: Phase II study of temozolomide (TMZ)-based chemo-radiotherapy (RT) regimen for high risk low grade gliomas (LGGs): preliminary results including quality of life (QoL) and neurological function (NCF). Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy. *Neuro Oncol.* 15(Suppl. 3), iii77, Abstract MR-009 (2013).
- Reijneveld JC, Bottomley A, Taphoorn MJB *et al.* Health Related Quality of Life results from temozolomide chemotherapy vs. radiotherapy in molecularly characterized (1p loss) low-grade glioma: a randomized Phase III Intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC22033–26033). *Neuro Oncol.* 15(Suppl. 3), Late-breaking abstract LB-004 (2013).
- Omuro A, Abrey L, Raizer J *et al.* Temozolomide followed by high-dose chemotherapy and autologous stem cell transplant (HDC-ASCT) for newly diagnosed anaplastic oligodendroglioma (AO): can radiotherapy be deferred? *Neuro Oncol.* 15(Suppl. 3), iii125, Abstract NO-108 (2013).

- 15 van den Bent M, Erdem L, Gorlia T *et al.* Identification of anaplastic oligodendroglioma patients benefiting from adjuvant PCV chemotherapy using the Illumina platform: a further report from EORTC 26951. *Neuro Oncol.* 15(Suppl. 3), iii152–iii153, Abstract OM-070 (2013).
- 16 Chinot O, Wick W, Mason W *et al.* Final efficacy and safety results from AVAglio, a Phase III trial of bevacizumab (BEV) plus temozolomide (TMZ) and radiotherapy (RT) in newly diagnosed glioblastoma (GBM). *Neuro Oncol.* 15(Suppl. 3), iii105–iii106, Abstract NO-031 (2013).
- 17 Taphoorn MJ, Henriksson R, Bottomley A *et al.* Health related quality of life (HRQOL) analyses in the AVAglio study, a randomized, placebo controlled Phase III trial of bevacizumab, temozolomide and radiotherapy in newly diagnosed glioblastoma. *Neuro Oncol.* 15(Suppl. 3), iii232, Abstract SM-029 (2013).
- 18 Gilbert M, Pugh S, Won M *et al.* RTOG 0825: primary outcome results from a Phase III randomized, placebo controlled trial evaluating bevacizumab in newly diagnosed glioblastoma. *Neuro Oncol.* 15(Suppl. 3), iii109, Abstract NO-046 (2013).
- 19 Armstrong TS, Won M, Wefel JS *et al.* Comparative impact of tumor and treatment on patients reported outcomes (PROs) in patients with glioblastoma (GBM) enrolled in RTOG 0525. *Neuro Oncol.* 15(Suppl. 3), iii226, Abstract SM-003 (2013).
- 20 Wefel JS, Pugh S, Armstrong T *et al.* Longitudinal analysis of neurocognitive outcome in patients with glioblastoma (GBM) enrolled in RTOG 0825. *Neuro Oncol.* 15(Suppl. 3), iii97, Abstract NC-021 (2013).
- 21 Herrlinger U, Schafer N, Steinbach J *et al.* Bevacizumab, irinotecan and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, *MGMT* non-methylated glioblastoma patients: updated results from the randomized multicenter GLARIUS trial. *Neuro Oncol.* 15(Suppl. 3), iii77, Abstract MR-011 (2013).
- 22 Nabors LB, Fink KL, Mikkelsen T *et al.* Cilengitide in combination with standard treatment for patients with newly diagnosed glioblastoma with unmethylated O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter: key results of the open label, controlled, randomized Phase II CORE study. *Neuro Oncol.* 15(Suppl. 3), iii80, Abstract MR-021 (2013).
- 23 Stupp R, Hegi ME, Gorlia T *et al.* Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma and methylated O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter: key results of the multicenter, randomized, open label, controlled, Phase 3 CENTRIC study. *J. Clin. Oncol.* 31(Suppl.), Abstract 2009 (2013).
- 24 Taal W, Oosterkamp H, Walenkamp A *et al.* A randomized Phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: the Dutch BELOB trial. *Neuro Oncol.* 15(Suppl. 3), iii83, Abstract MR-035 (2013).
- 25 Bevacizumab and Lomustine for Recurrent GBM. www.cancer.gov/clinicaltrials/EORTC-26101
- 26 Omuro A, Chinot O, Taillandier L *et al.* Multicenter randomized Phase II trial of methotrexate and temozolomide versus methotrexate, procarbazine, vincristine and cytarabine for newly diagnosed primary CNS lymphoma (PCNSL) in the elderly: an ANOCEF/GOELAMS intergroup trial. *Neuro Oncol.* 15(Suppl. 3), iii124–iii125, Abstract NO-107 (2013).