Neuro-oncology: a selected review of ASCO 2014 abstracts

Marc C Chamberlain*

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ASCO, the American Society of Clinical Oncology, is the largest clinical oncology meeting in the USA that meets annually and is a venue at which new cancer clinical trials and research data are presented. The ASCO 2014 CNS tumors section comprising 2 days of posters and oral presentations and over 100 abstracts provides an up-to-date overview of neuro-oncology, including both metastatic diseases of the CNS as well as primary brain tumors. This brief review selectively highlights presentations presented at this years meeting in an organizational manner that will hopefully provide a portrait of a large and multifaceted meeting.

Metastatic disease to the CNS

• Parenchymal brain metastases

Preusser presented data suggesting that in parenchymal brain metastases (BM), quantification of tumor infiltrating lymphocytes (TILs) in 111 BM predicts for survival (more is better, i.e., longer survival with increased TILs) and cerebral edema (less is more, i.e., more cerebral edema in tumors with fewer TILs) [1].

• Leptomeningeal metastases

In a retrospective study by LeRhun of 60 patients with breast cancer-related leptomeningeal metastases (LM), the majority treated with intra-CSF chemotherapy underwent a review of pretreatment MRI (brain and spine) to assess whether the pattern of MRI disease (seen in >70% of all patients) was prognostic [2]. Median overall survival (OS) was 4 months. The only MRI pattern that predicted for outcome was focal linear contrast enhancement, a pattern that was prognostic for better outcome. These results suggest that pretreatment neuroradiographic assessment of leptomeningeal disease burden has prognostic significance and may be predictive of OS.

Primary brain tumors

• Primary CNS lymphoma

Korfel presented long-term follow-up data (median follow-up 81 months) from the German randomized Phase III trial in newly diagnosed primary CNS lymphoma (PCNSL) [3]. In patients with a complete response (CR) to high-dose methotrexate (HD-MTX), patients were randomized to either observation only or consolidative whole-brain radiation therapy (RT; WBRT). In patients with a CR, progression-free survival (PFS) or OS was not improved with the inclusion of WBRT.

KEYWORDS

• ASCO 2013 • CNS tumor abstracts • primary brain tumor • secondary brain tumor

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

In patients with a partial response or less to HD-MTX, WBRT afforded a modest improvement in PFS, but not OS. The authors conclude that the PFS advantage afforded by WBRT needed to be balanced with the delayed late neurotoxicity of WBRT.

• Meningiomas

Norden reported on a Phase II trial of the long-acting somatostatin analogue, pasireotide LAR, for radiation-refractory recurrent meningiomas separable into two cohorts (Grade 1 meningiomas; $n = 16$ and Grade 2 and 3 meningiomas; $n = 18$) [4]. Although the trial was reported as negative, interpretation conflicts with the recently published RANO response criteria for recurrent meningioma suggesting an active agent having a 6-month PFS of 29% or greater in Grade 1 and 26% in Grade 2 and 3 meningiomas. Currently there is a paucity of drugs active for this disease.

• Gliomas

Low-grade gliomas

Up-front trials

Buckner presented recent and mature data from the RTOG 9802 randomized trial comparing RT to RT + procarbazine, lomustine, vincristine (PCV) chemotherapy in adults with high-risk low-grade glioma (LGG) as defined by the study (age >40 years or incomplete resection) [5]. When reported in 2012, the study data suggested a benefit in PFS, but not for OS; however, at that time only 35% of patients had died and follow-up was 5.7 months. In the current report wherein both PFS (4 vs 7.8 years) and OS (7.8 vs 13.3 years) were significantly improved in the RT + PCV arm, mean follow-up was 11.9 years and 55% of patients had died. Furthermore, as the RTOG data matures as suggested by the 10-year OS data, the difference between treatment arms continues to widen further favoring the RT + PCV treatment. This practice changing study suggests that the majority of patients with LGG would benefit from combination therapy as only a minority of patients are able to undergo an image verified complete resection and thereby have deferred further therapy. Not reported was a molecular analysis, particularly with respect to the now prognostic p53, IDH-1 and ATRX mutations, as well as the presence of the 1p19q codeletion or g-CIMP. Nonetheless, the RTOG 9802 high-risk LGG data remarkably recapitulates the data from trials in 1p19q

codeleted anaplastic gliomas, suggesting differences between these WHO grade gliomas is likely best determined by molecular interrogation rather than histology. Still unanswered is whether TMZ may substitute for PCV in the adjuvant treatment of LGG, a similar dilemma seen in the management of anaplastic gliomas.

Lautenschlaeger, using a dataset of 756 gliomas, developed a prognostic six-gene signature for WHO Grade 2 and 3 gliomas [6]. The six-gene classifier was validated in the TCGA and an institutional independent dataset. By report the six-gene classifier better predicted 3-year survival than histology, grade or IDH-1 mutational status. Not shared was the composition of the six-gene classifier, nor were any data presented regarding 1p19q codeletion or ATRX mutational status.

Anaplastic gliomas

Salvage trials

Wiestler re-examined molecular markers in the German NOA-04 trial using a novel platform (Illumina Infinium Human Methylation 450 beadchip array; HM450) that simultaneously assessed MGMT, IDH1, 1p19q and g-CIMP and compared results with individual assays currently performed for these same biomarkers [7]. Overall, their data suggest that HM450 analysis may be able to replace individual marker tests for routine assessment of anaplastic gliomas.

Glioblastoma

Up-front trials

Wen presented a randomized Phase II trial in 124 patients with newly diagnosed glioblastoma (GBM) treated with standard of care (RT + temozolomide [TMZ] followed by post-RT TMZ) with an active or placebo dendritic vaccine – ICT-107. The ICT-107 vaccine is comprised of six tumor-specific antigens (MAGE, HER-2, Aim-2, TRP-2, gp100 and IL13 α 2) and was administered following RT in 4 weekly doses (induction) followed by post-RT TMZ and maintenance vaccine [8]. Importantly, patients were eligible for trial only if following surgery there was evidence of a complete or near complete resection. Although data are immature, there appears to be both a PFS and OS benefit to the active ICT-107 arm, a first for a placebo-controlled randomized trial vaccine-based study in GBM.

Phillips undertook an analysis of 349 patients in the AVAglio trial to determine if there was

a molecularly defined subgroup identified by nanostring gene expression (transcriptome) analysis that derived benefit from up-front treatment of GBM with bevacizumab [9]. Dividing molecular subgroups into proneural (28% overall), mesenchymal (40%) and proliferative (16%) as previously described showed in multivariate analysis that the IDH wild-type proneural group (excluding the IDH mutant group due to small numbers) derived benefit in both PFS and OS when treated with bevacizumab when compared with placebo. These data await confirmation in an independent data set and may, if confirmed, highlight a molecularly defined group of newly diagnosed GBM that benefit from up-front bevacizumab.

Wick presented data from a randomized EORTC 26082/22081 trial in 111 patients with an unmethylated GBM comparing standard RT + TMZ followed by post-RT TMZ to RT and concurrent and adjuvant temsirolimus, an intravenously administered mTOR inhibitor. There was no significant benefit (defined by OS at 12 months) seen when comparing temsirolimus to TMZ [10]. These data further emphasize the unmet need of new therapy for this large cohort of newly diagnosed GBM. Raizer reported on a another single-arm Phase II trial in MGMT unmethylated newly diagnosed GBM wherein 115 patients were treated with RT + TMZ followed by bevacizumab and erlotinib, an epidermal growth factor receptor inhibitor post-RT. Although well tolerated when compared with historical controls, no improvement in either PFS or OS was observed [11].

Tanguturi presented retrospective data comparing treatment of elderly patients (defined as >65 years of age) with GBM using a variety of RT schema with or without TMZ [12]. The data suggests a modest improvement with hypofractionated RT (40 Gy in 15 fractions) compared with standard RT (60 Gy in 30 fractions) when combined with TMZ. Still unclear is the contribution of TMZ in this regimen and a primary question of the large randomized NCI Canada and EORTC elderly GBM study that compares hypofractionated RT with or without TMZ.

Soffietti reported on a study of 58 patients, primarily GBM, in whom a comparison of MGMT promoter methylation status was determined by paired tumor and plasma analysis showing a strong concordance between both methods of analysis [13]. This alternative method of MGMT determination if validated may permit assay in

all patients, notwithstanding limited tumor tissue.

Berghoff analyzed 117 patients with GBM and determined expression of PD1 and PD-L1. PD1 expression (determined by immunohistochemistry) was seen in 15% of all GBM and seen on TILs. By contrast, PD-L1 was expressed on nearly all GBM tumor cells (86%) following first resection. No attempt was made to quantify expression levels of either PD1 or PD-L1, however the results suggests immune check point inhibition may be a biologically relevant target in GBM [14].

Salvage trials

Galanis presented the data from a Phase II Alliance trial of 107 patients that assessed the utility of vorinostat, a histone deacetylase (HDAC) inhibitor, when added to standard of care (RT + TMZ followed by TMZ) in newly diagnosed GBM patients [15]. The rationale was twofold: first, vorinostat has modest activity in recurrent GBM, and second, vorinostat is a radiosensitizing agent. When compared with historical controls there was no added benefit to vorinostat, notwithstanding tolerable added toxicity.

Huang reanalyzed data from the BRAIN trial in first recurrent GBM comparing bevacizumab with or without irinotecan and in particular assessing whether evaluation using Macdonald response criteria versus RANO criteria affected determination of objective response rate (ORR) or PFS [16]. The inclusion of T2/FLAIR assessment in the RANO criteria results in a small difference in median PFS, but no significant difference in ORR. The associations of ORR and PFS with OS using the RANO criteria at 6 months and earlier time points following therapy potentially support their possible roles as surrogates for OS.

Platten reported on a randomized Phase II trial in recurrent GBM considered candidates for re-radiation (tumor <4cm in diameter, good performance status) comparing re-RT (36 Gy in 2 Gy fractions) with or without the radiation-sensitizing agent APG-101, a CD95-ligand-binding fusion protein administered weekly and intravenously [17]. 84 patients were treated and 6-month PFS was 3.8% in the re-RT only arm compared with 20.7% in the APG-101 + re-RT arm. Furthermore, a greater benefit was seen in the combination arm in tumors with MGMT promoter methylation. This small trial suggests

further exploration of APG-101 is warranted and raises the question of whether there is value to re-RT only in recurrent GBM.

Butowski presented data from a Phase 0/I trial in recurrent GBM (n = 38) of the selective CSF1R, KIT and FLT3 kinase small-molecule oral inhibitor, PLX3397 [18]. CSF1R is expressed on microglia/macrophages and tumor cells within GBM. Many glioma cell lines express the CSF1R ligands, CSF-1 and IL-34 and the KIT ligand, SCF, and depletion of microglia/macrophages in preclinical GBM models reduces tumor burden and spread. The results demonstrate that PLX3397 is a potent inhibitor of tumor-associated macrophages and microglia, readily entered GBM, and as a single agent showed no significant improvement in PFS. A trial is underway assessing PLX3397 in newly diagnosed GBM to establish efficacy when used in combination with RT + TMZ.

Tabatabai presented data on the DIRECTOR study (prematurely closed secondary to loss of sponsor) that compared re-challenge with TMZ in patients progressing on standard post-RT TMZ (5/28 schedule) [19]. 105 patients were accrued to study and randomized to one of two dose-dense TMZ regimens (7/14 or 21/28). There was no significant advantage in either TMZ arm (median time to treatment failure was <60 days in both), however patients with MGMT methylated tumors manifested significantly better survival suggesting a benefit to

re-challenge with TMZ in this defined cohort. Not clear from this study however is whether re-challenge with TMZ requires a dose dense regimen as standard dose TMZ is likely as effective in the recurrent MGMT hypermethylated population.

Lee presented the results of a placebo-controlled randomized trial of armodafinil for fatigue (a symptom-targeted therapy) in 77 gliomas (mostly GBM) undergoing RT [20]. Armodafinil is a second-generation nonamphetamine stimulant used and indicated primarily for primary sleep disorders. Fatigue is common in patients receiving RT and was measured in the trial by FACIT-F fatigue subscale. There was a nonstatistically significant trend for benefit in the armodafinil arm, a result that mirrors data from other studies using psychostimulants in cancer treatment-related fatigue. There is an ongoing Alliance randomized Phase III trial for clinically stable patients with GBM post-RT and manifesting severe fatigue assessing armodafinil.

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