Neuro-oncology: a selected review of ASCO 2015 abstracts

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ASCO, the American Society of Clinical Oncology, is the largest clinical oncology meeting that meets annually in the USA and is a venue at which new cancer clinical trials and research data are presented. The ASCO 2015 CNS tumors section comprising 3 days of posters and oral presentations and over 70 abstracts provides a contemporary summary of neuro-oncology including metastatic diseases of the CNS as well as primary brain tumors. This brief review selectively highlights presentations from this meeting in an organizational manner that reflects clinically relevant aspects of a large and multifaceted meeting.

Metastatic disease to the CNS

• Parenchymal brain metastases

Brown *et al.* presented in the ASCO plenary session the results of the Alliance N0574 randomized Phase III trial (n = 213) in patients with 1–3 brain metastases (BM; any cancer though primarily lung and each lesion <3 cm in diameter) comparing stereotactic radiosurgery (SRS) with or without whole brain irradiation (WBRT) [1]. Despite no difference in overall survival (OS), the SRS only arm showed improvement in quality of life measures as well as neurocognitive function at 3 months, both prespecified primary end points. Notably, however, N0574 did not report neurological-specific survival; relevant as CNS-directed therapy does not improve OS as the majority of patients succumb to progressive systemic disease. Furthermore, patients did not receive any systemic therapy emphasizing the minimal systemic disease burden in this treatment group. Lastly, the study further documents SRS only arm had a nearly twofold increase in recurrent BM necessitating careful clinical and imaging follow-up and more frequent retreatment of brain as compared with the SRS + WBRT arm. Consequently, the generalizability of this study is limited in patients with BM.

Chabot *et al.* reported results of a randomized, global, multicenter study of WBRT plus veliparib or placebo in patients with BM from non-small-cell lung cancer [2]. Veliparib is a potent, orally bioavailable PARP inhibitor that crosses the blood–brain barrier and in early clinical trials showed promising efficacy as a radiation synergizing agent. There was, however, no difference in OS (≈6 months) between the treatment arms.

• Leptomeningeal metastases

A retrospective study by Morikawa *et al.* of 318 patients with breast cancer-related leptomeningeal metastases (LM) (62% Her2 positive) and treated with radiotherapy (RT) only (64%) or

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high-dose methotrexate (20%), demonstrated a median OS of 3.5 months and an approximately 20% 1-year survivorship [3]. Cranial only site of LM (43%), good performance status and control of extraneural disease were associated with improved outcome. Lin *et al.* using a rare cell capture technique prospectively validated enumeration of CSF circulating tumor cells (CTC) in 62 patients with suspected LM. Detection of CTC by the rare cell capture technique was sensitive and appeared superior to both CSF cytology and MRI for establishing a (pathological) diagnosis of LM [4].

Primary brain tumors

• Primary CNLS lymphoma

Roth *et al.* presented long-term survival in patients with primary CNLS lymphoma (PCNSL) enrolled in the German SG1 trial [5]. Of 459 patients with sufficient data quality, 89 patients (≈20%) were identified who had survived for 5 years or more after surgery and diagnosis of PCNSL. Within the group of long-survival patients, age at diagnosis was the only prognostic factor for conditional survival from 5 years on. Tabouret *et al.* reported on patterns of relapse in patients enrolled the French ANOCEF study with PCNSL [6]. Relapse in the brain involved the initial enhancing site, a site at distance, or both in 46, 40 and 14%, respectively. At baseline, nonenhancing T2-FLAIR hypersignal lesions at distance from the enhancing tumor site were detected in 18 patients (23%), among whom 16 (88%) displayed a marked decrease (>50%) after chemotherapy consistent with their neoplastic nature. Among these 18 patients, ten relapsed, and the initially nonenhancing T2-FLAIR lesions corresponded to the site of an enhancing relapse in half of them. The authors conclude that relapse at a distance from the initial enhancing tumor is frequent and may occur in the area of nonenhancing T2-FLAIR radiographically noncontiguous with enhancing lesions.

• Meningiomas

Grimm *et al.* reported on a Phase II trial of bevacizumab for radiation refractory recurrent meningioma separable into three cohorts (Grade 1 meningioma, n = 15; Grade 2, n = 22 and Grade 3, n = 13) [7]. 6-month progression-free survival (PFS-6), median PFS and median OS were 87%, 22.5, 35.6 months for Grade 1; 77%, 15.3 months, not reached for Grade 2;

and 46%, 3.7, 12.4 months for Grade 3. The authors concluded that treatment with bevacizumab commonly leads to disease stabilization and when compared with a recent meta-analysis of treatments in a similar population the results appear promising.

• Gliomas

Low-grade gliomas

Up-front trials

Baumert *et al.* presented a subgroup analysis of the randomized EORTC Phase III trial (22033-26033) in high-risk low-grade gliomas (n = 477) comparing RT only to temozolomide (TMZ) only with deferred RT. IDH1 and IDH2 mutations were detected in 83 and 2.8% [8]. Codeletions of 1p/19q were identified in 33%. Methyguanine methyltransferase (MGMT) was methylated in 90% of which 86% were isocitrate dehydrogenase (IDH) mutant. Mutation of the IDH regardless of 1p/19q codeletion was a positive prognostic factor. Exploratory analysis revealed that patients with IDH mutated and non-codeleted tumors had a shorter PFS after treatment with TMZ than after RT. With limited events in the codeleted cohort, no such difference was evident though the data remain immature.

Two papers were presented that discussed molecular classification of WHO Grade II and III tumors that in both instances was superior with respect to diagnosis and prognostic prediction relative to histological classification [9,10]. Suzuki in a large Japanese consortium performed whole gene sequencing in 755 low-grade and anaplastic gliomas and identified three major groups; IDH wild-type subdivided into two categories, a glioblastoma (GBM)-like subgroup and a non-GBM subgroup both with impoverished survival and a IDH-mutated supergroup subdivided into two groups, 1p19q codeleted group that was coassociated with telomerase reverse transcriptase (TERT) promoter mutation, CIC, FUBP1 and NOTCH1 and associated with the best prognosis and the non-1p19q group associated with the TP53 and ATRX mutations and an intermediate prognosis. A multiregional multiple time point sampling analysis demonstrated a mutational order consistent with clonal evolution and showing increasing tumor heterogeneity both spatially and temporally with intersecting mutational evolutionary branch nodes. Weller *et al.* for the German Glioma Group reported on a comparison between genomic and gene

expression profiling in 137 low-grade and anaplastic gliomas [10]. Genomic profiling identified five distinct glioma groups, including three IDH1/2 mutant and two IDH1/2 wild-type groups. Three major prognostic groups with characteristic genomic aberrations were identified including IDH mutant and 1p19q codeleted tumors (best prognosis), IDH wild-type and GBM-like alterations (TERT promoter mutations, gain of chromosome 7q and loss of chromosome 10q) had the worst outcome and IDH mutant and non-codeleted tumors with an intermediate prognosis. The authors conclude that DNA-based molecular subgrouping stratified patients into distinct prognostic groups better than histological classification and the addition of gene expression data did not further improve prognostic stratification.

Anaplastic gliomas

Up-front trials

Chang *et al.* reported on the prematurely closed (due to poor accrual) RTOG trial 9813 that compared in newly diagnosed anaplastic astrocytomas RT + TMZ versus RT + nitrosourea-based (BCNU or CCNU) chemotherapy [11]. 197 patients were randomized in which there was no difference in either median PFS or OS (3.9 vs 3.8 years). There was increased toxicity seen in the nitrosourea chemotherapy arm; however, the study concluded there appeared to be no significant difference in the two treatment arms.

Glioblastoma

Up-front trials

Stupp *et al.* presented early follow-up data in the EF-14 study of 700 patients with newly diagnosed GBM randomized 2:1 to standard of care (SOC; RT + TMZ followed by TMZ) with or without the tumor-treating fields device (TTF; Novocure) [12]. Progression-free survival was 7.1 months for TTF versus 4.2 months for TMZ only. Similarly, OS was improved for the TTF arm (19.4 vs 16.6 months) as was 2-year survival (43 vs 29%). The authors concluded TTF should now be considered a new SOC for GBM in the up-front setting notwithstanding the immaturity of the data (median follow-up is 12 months) and the confounding influence regarding intensive supportive care in the TTF arm that is in effect early introduction of palliative care. Lastly, the issue of expense (≈US\$23,000 per month) and the frequent failure of coverage by third-party insurers was not been addressed.

Two Phase II immunotherapies, gene-mediated cytotoxic therapy and an autologous heat-shock protein peptide vaccine, were presented that were used concurrently with SOC in newly diagnosed GBM [13,14]. Aguilar reported on the Phase II trial (n = 48) of local delivery of a gene-modified adenovirus containing thymidine kinase which transfects the GBM and when treated subsequently with oral valacyclovir results in a modest improvement in OS when compared with historical controls [13]. Bloch *et al.* presented data regarding response to the personalized tumor lysate prepared heat-shock protein–peptide vaccine (n = 46), where when compared with historical controls there was an improvement in both PFS and OS [14]. Importantly, the best response to therapy was seen in GBM patients in whom circulating monocytes displayed high expression of PDL-1, a possible novel biomarker for vaccine efficacy.

Galanis and colleagues for the Alliance reported on the N0877 Phase II trial using dasatinib, a small-molecule inhibitor of Src, in conjunction with SOC in newly diagnosed GBM [15]. The combination of the Src kinase inhibitor dasatinib with standard RT/TMZ did not improve the outcome of newly diagnosed GBM patients as compared with standard therapy alone.

Salvage trials

Practice changing were results from the Australian CABARET-randomized trial comparing BEV to BEV + carboplatin [16]. This trial although negative did randomize patients (n = 48) following progression on BEV to either continuation of BEV in conjunction with physician-determined cytotoxic chemotherapy or discontinuance of BEV and use of physician-determined cytotoxic chemotherapy. There were no radiological responses in either arm, median PFS (BEV vs no BEV) was 1.8 versus 2.0 months and median OS was 3.4 versus 3.0 months. The authors conclude that continuing BEV after progression does not improve PFS or OS in this prospective study.

Several other recurrent GBM single-arm Phase II trials, all negative, were conducted in recurrent GBM, all of which added a novel targeted agent (e.g., dasatinib, vorinostat, onartuzumab, buparlisib and carboxyamidotriazole) to BEV [17–22]. Currently, the addition of lomustine (CCNU) as shown in the Dutch BELOB trial and confirmed in a small randomized Phase II trials reported by Shia-Pei remains the most active BEV combination therapy for recurrent GBM [23].

Reardon *et al.* presented survival data from the ReACT trial, wherein BEV naïve patients with recurrent GBM (that were EGFRviii mutated) were treated with BEV alone or BEV + the EGFRviii peptide vaccine, rindopepimut [24]. Although the trial failed to meet its primary end point (PFS-6 >40%), outcome was encouraging for the experimental arm with respect to overall radiographic response (24 vs 17%), PFS-6 (27 vs 11%) and OS (12 vs 8.8 months). Further confirmation is expected regarding the vaccine's efficacy from the up-front ACT 4 trial in GBM.

Weller and colleagues presented data from the German DIRECTOR trial that compared two different dose-intensified TMZ regimens in 105 patients [25]. In patients undergoing resection before study entry (n = 71) and who entered the trial with smaller tumor volumes, there was no benefit in survival when compared with patients entering study without reoperation, data congruent from a previously reported study by UCSF. The authors suggest however survival benefit may be seen in patients who undergo an image-verified complete resection. This study again raises the question of whether reoperation is of benefit in patients with recurrent GBM.

Conclusion

Several potentially practice changing trials were presented this year at ASCO most notably SRS without WBRT for oligometastatic (1–3) parenchymal BM, the apparent utility of the TTF device for newly diagnosed GBM as per the EF14 trial, discontinuance of BEV following progression on BEV based on the prospective CABARET trial and the apparent efficacy of the EGFRviii vaccine in recurrent GBM when combined with BEV per the ReACT clinical trial. Lastly, the increasing recognition of molecular markers to differentiate categories of WHO Grade II and III gliomas provides diagnostic clarity superior to histopathology as well as predictive and prognostic utility will increasing influence clinical trial design and clinical practice.

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