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Neuro-oncology: a selected review of ASCO 2013 abstracts

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The American Society of Clinical Oncology (ASCO) is the largest clinical oncology meeting in the USA that meets annually, and is an exciting forum in which new cancer clinical trials and research data are presented. The ASCO 2013 CNS tumors section comprising of 3 days of posters, oral presentations and over 100 abstracts provided a current overview of neuro-oncology, including both metastatic diseases of the CNS, as well as primary brain tumors. This brief overview selectively highlights presentations featured at this year's meeting in a manner that will hopefully provide a portrait of a large and multifaceted meeting.

Metastatic disease to the CNS

■ Parenchymal brain metastases

Several abstracts were presented; the most notable utilizing an oral histone deacetylase (HDAC) inhibitor, vorinostat, as a radiosensitizer in a Phase I study in combination with whole brain radiotherapy (WBRT). The study suggested safety and feasibility of this combinatorial therapy [1]. The Phase I study followed preclinical studies demonstrating vorinostat as a potent radiosensitizer. Based upon the results of this Phase I study, a larger Phase II study is being initiated to determine whether the laboratory documented radiosensitization of HDAC inhibitors augments WBRT for the treatment of patients with brain metastases. The other notable trial was a randomized Phase III trial of WBRT in 468 patients with non-small-cell lung cancer and brain metastases with or without topotecan [2]. Post-WBRT treatment was at the treating

physician's discretion. There was no difference in overall survival achieved by the addition of topotecan (4 months with topotecan and WBRT vs 3.6 months with WBRT only).

■ Leptomeningeal metastases

A retrospective study of 240 patients with leptomeningeal metastases included 165 patients with solid tumors, 50 with lymphoma and 25 with leukemia. The study demonstrated that, following pretreatment neuraxis imaging that utilized brain and complete spine MRI and a radioisotope cerebrospinal fluid flow study, an increased volume of leptomeningeal metastases, as well as uncorrected cerebrospinal fluid radioisotope flow studies, impacted survival negatively [3]. These results suggest that pretreatment neuro-radiographic assessment of leptomeningeal disease burden has prognostic significance and may be predictive of overall survival.

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Primary brain tumors

■ Primary CNS lymphoma

A multicenter French randomized Phase II trial compared high-dose methotrexate (HD-MTX) and temozolomide (TMZ) to HD-MTX, procarbazine, vincristine and high-dose cytarabine (MPV-A) in 98 elderly patients with primary CNS lymphoma [4]. All efficacy end points (progression and overall survival) favored the MPV-A arm, which was recommended for further development. It is not clear from this study how different and probably more often utilized HD-MTX treatment platforms, for example HD-MTX and rituximab, perform when compared with MPV-A. A retrospective abstract from Johns Hopkins Hospital (MD, USA) compared HD-MTX to HD-MTX and rituximab in 81 patients with primary CNS lymphoma and showed a higher response rate with combination therapy, suggesting a potential benefit of this regimen compared with single-agent HD-MTX [5].

■ Gliomas

Low-grade gliomas

Up-front trials

A large, randomized European Organization for Research and Treatment of Cancer (EORTC) Phase III study of symptomatic and progressive low-grade gliomas (n = 477 patients) compared TMZ (dose dense schedule of 21 treatment days every 28 days) to radiotherapy (RT; 50.4 Gy total dose) with the prespecified end point that TMZ was superior [6]. Regardless of histology or 1p deletion status, in all patients TMZ was inferior to RT both with respect to progression-free (40 vs 47 months) and overall survival (74 months vs not yet reached) recognizing that the data are currently immature.

The Radiation Treatment Oncology Group (RTOG) reported on a single-arm Phase II study of RT with concurrent and post-RT TMZ in patients with high-risk low-grade gliomas as defined by the EORTC [7]. The 3-year overall survival was superior to that reported for historical controls (73 vs 54%), suggesting TMZ-based chemoradiotherapy may be more efficacious than RT only in this patient group. An ECOG trial currently open and accruing

is testing this supposition in a randomized Phase III trial.

Anaplastic gliomas

Up-front trials

Two abstracts were notable regarding molecular prognostication of anaplastic glioma (AG) [8,9]. In a re-analysis of 115 patients in the EORTC 26951 study of anaplastic oligodendroglial tumors, the Illumina® (CA, USA) methylation profiling platform provided superior identification of patients likely to respond to RT plus procarbazine, lomustine and vincristine chemotherapy, as determined by MGMT promoter methylation and CpG island hypermethylated phenotype [8].

In a retrospective study of 184 patients with anaplastic astrocytoma from the Mayo Clinic (MN, USA), *IDH1* mutation status was prognostic for overall survival and independent from other recognized prognostic variables [9]. An almost fivefold increase in overall survival was seen in patients with *IDH1* mutation versus those with wild-type *IDH1* (117 vs 23 months). Similarly, receipt of adjuvant TMZ improved overall survival. The currently open and accruing EORTC study for newly diagnosed uni- or non-deleted AG (CATNON), in which *IDH1* mutational status is being collected prospectively, will better define the significance of *IDH1* as it relates to both survival and response to treatment in AG.

Glioblastoma

Up-front trials

Five up-front trials utilizing bevacizumab (BEV) were presented and together represent practice changing studies [10–14]. Similar in design and outcome were the randomized Phase III RTOG 0825 (n = 637 patients) and AVAglio (n = 921 patients) studies that compared standard-of-care RT plus TMZ (SOC) with or without BEV [10,11]. Both trials failed to show a benefit in overall survival (AVAglio: 16.8 vs 16.9 months; RTOG: 16.1 vs 16.6 months) notwithstanding an improvement in progression-free survival (AVAglio: 6.2 vs 10.6 months; RTOG: 7.3 vs 10.3 months). In part the failure to demonstrate a survival benefit in the BEV arm represents a crossover effect wherein 30–40% of patients in the SOC arm were

treated with BEV at recurrence. By contrast, the randomized Phase II German GLARIUS trial compared SOC with or without BEV plus irinotecan in 182 unmethylated MGMT promoter glioblastoma (GBM) patients [12]. GLARIUS demonstrated both a progression-free (6 vs 9.74 months) and overall survival advantage (14.8 vs 16.6 months). Concordant with the RTOG and AVAglio trials was the Brain Tumors Trial Collaborative (BTTC) single arm Phase II study of post-RT BEV and erlotinib in 48 patients with unmethylated GMB, in which progression-free and overall survival were 7.3 and 14.2 months, respectively [13]. Lastly, the French ANOCEF consortium assessed TMZ and BEV (and deferred RT) in 66 elderly patients (defined as age >70 years) with GBM in which performance status was compromised and who underwent biopsy only [14]. Median survival (4 months) was similar to a previous ANOCEF study that compared TMZ only to best supportive care suggesting no added benefit with the addition of BEV. In aggregate, these trials do not support the use of BEV in the up-front setting and consequently TMZ-based chemoradiotherapy remains as the best current therapy for newly diagnosed GBM in nonelderly patients. A major point of discussion were the differences in patient-reported outcomes when comparing the RTOG 0825 trial (no benefit seen in the BEV arm with respect to a health-related quality of life instrument, the MD Anderson symptom inventory or neurocognitive function outcome) to the AVAglio trial (a benefit seen in the BEV arm regarding health-related quality of life) [15–17]. These differences appeared to be more methodological and likely relate to the manner of analysis. The AVAglio trial group also presented data demonstrating a difference in the incidence of pseudoprogression (BEV arm 2.2% vs SOC arm 9.3%) but no difference in the pattern of radiographic disease progression when comparing both arms of the trial [11]. Lastly, RTOG 0825 presented data regarding prospective utility of the nine gene assay, which failed to be prognostic in either treatment arm [18].

The last randomized trial presented of note was CENTRIC, a trial comparing SOC with or without the anti-integrin, cilengitide in promoter-methylated GBM

patients [19]. No difference was seen in either progression-free (13.5 vs 10.7 months) or overall survival (26.3 months in both arms). Although there was no toxicity associated with cilengitide, it is unlikely this agent will be further pursued in neuro-oncology given the lack of benefit in both newly diagnosed and recurrent GBM.

In a study from the German Glioma Network, two groups of patients with GBM were compared; 69 patients that were defined as long-term survivors (LTSs: >3-year survivorship) and 259 controls (survivorship <3 years) [20]. The rate of *IDH1/2* mutations in the LTS cohort was 34% compared with 4.3% in the control group, suggesting a large fraction of GBM LTSs are characterized as secondary GBM. However, the molecular characterization of the majority of GBM LTSs with wild-type *IDH1/2* remains to be defined.

Salvage trials

Two randomized Phase II trials in first recurrent GBM were presented: the Dutch BELOB and the Australian CABARET trials [21,22]. The BELOB trial (n = 153 patients) compared lomustine (CCNU) to BEV, and the combination of CCNU plus BEV and as such constitutes the first BEV trial in recurrent GBM to compare BEV to a SOC agent, lomustine. Progression-free survival at 6 months favored the combination arm (11 vs 18 vs 41%) as did median overall survival (8 vs 8 vs 11 months) [22]. These results raise the question of whether there is a survival advantage to BEV in recurrent GBM that will be further investigated in the larger randomized Phase III EORTC 26101 trial using similar treatment arms.

The CABARET trial compared BEV with or without carboplatin in 122 patients with first recurrent GBM [21]. There were no differences seen in either progression-free survival at 6 months (26 vs 24%) or median overall survival (6.9 vs 6.4 months). The CABARET trial re-iterates that there is no added benefit in treating patients with recurrent GBM with BEV and a cytotoxic chemotherapy as compared with BEV alone. A similar conclusion was reached in a study evaluating adding panobinostat, an oral HDAC inhibitor to BEV in recurrent GBM [23].

Two trials in patients with recurrent GBM progressing on BEV evaluated novel agents (sorafenib and temsirolimus in the Alliance study; nintedanib, a triple receptor tyrosine kinase inhibitor in the Dana Farber Cancer Center study) [24,25]. Both studies confirmed the current consensus that there is not an effective treatment for patients with recurrent GBM who progress on BEV (no objective responses, median progression-free survival <2 months and median survival 3–5 months) and consequently the best treatment for such patients remains undefined.

Four trials were presented (three Phase I and one Phase II) evaluating novel PI3K inhibitors (XL765, a combined PI3K and mTOR inhibitor; XL 147, BKM120 and PX866 all pan-PI3K inhibitors) in recurrent GBM [26–28]. Three studies (XL765, XL147 and BKM120) used a treat–resect–treat paradigm and demonstrated that all evaluated drugs penetrate tumor (up to 40% serum concentrations) and appear to have targeted effects on downstream signaling pathway components (decrease in pS6K and pAKT). This novel trial design provides clinically relevant pharmacokinetic and pharmacodynamic data regarding small molecule inhibitors with respect to their use in gliomas. The Canadian Phase II trial with PX-866 demonstrated 17% 6-month progression-free survival results similar to many other cytotoxic and targeted agents and considered inactive in recurrent GBM [28]. Another Phase II trial of the oral transforming growth factor β receptor inhibitor, LY2157299, suggested minimal single-agent activity in GBM [29]. In aggregate these small molecule inhibitor studies demonstrate limited single-agent activity and suggest combination therapy targeting multiple signaling pathways may be more effective assuming toxicity of combined therapy is not prohibitive.

A first-in-human study assessed and confirmed the safety of neural stem cells

transfected with cytosine deaminase injected into the brain surrounding the tumor, following re-resection of recurrent GBM, followed by oral 5-fluorocytosine [30]. The hypothesis was that cytosine deaminase-containing neural stem cells migrate into the tumor and the subsequent exposure to 5-fluorocytosine results in the enzymatic conversion to 5-fluorouracil with leakage of cytotoxic 5-fluorouracil into the surrounding tumor.

Conclusion

ASCO 2013 CNS tumors was dominated by discussions regarding BEV and its role in the management of glioblastoma. Aside from the GLARIUS study, all trials using BEV in the up-front setting (AVAglio, RTOG 0825, BTTC and ANOCEF supra vide) concur there is no role for the adjuvant use of BEV. Whether there is a benefit with up-front BEV with respect to patient-reported outcomes is more problematic owing to differing analytic methodologies amongst studies. The use of BEV in recurrent GBM was explored in the Dutch BELOB and Australian CABARET trials. The BELOB trial raised the question of whether BEV should be the only preferred treatment for recurrent GBM and suggested the combination of lomustine (CCNU) and BEV may be superior. This important question will be defined upon completion of the currently open and accruing EORTC 26101 study.

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