Conference Report

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American Society of Clinical Oncology 2021 Annual Meeting updates on primary brain tumors and CNS metastatic tumors

Archit B Baskaran[1], Priya Kumthekar[2,3], Amy B Heimberger[3,4] & Rimas V Lukas*[,2,3]

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[2]Department of Neurology, Northwestern University, Chicago, IL, USA
[3]Lou & Jean Malnati Brain Tumor Institute, Northwestern University, Chicago, IL, USA
[4]Department of Neurosurgery, Northwestern University, Chicago, IL, USA
*Author for correspondence: Rimas.lukas@nm.org

In this report, select key studies presented at the American Society of Clinical Oncology (ASCO) 2021 annual meeting are reviewed. Two major phase III randomized controlled trials were presented at the meeting: GEINO 1401 and EORTC 1709/CCTG CE.8. Both are reviewed in this report. Moreover, important phase II trials, including Alliance A0716701, and key phase I trials are included. All trials presented cover important advances in the understanding of primary brain tumor management. In addition, case series papers, trials in progress and select work on exploratory CSF biomarkers are reviewed. Altogether, research presented at ASCO 2021 highlights important advances in neuro-oncologic topics that may inform future research and practice.

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The American Society of Clinical Oncology (ASCO) held its annual meeting virtually 4–8 June 2021. A wide spectrum of health professionals and researchers participated in the meeting, covering all aspects of oncology. Highlights of the neuro-oncologic topics are reviewed here with a focus on clinical studies of primary brain tumors and cerebrospinal fluid biomarkers in central nervous system metastases. Due to the broad scope of the meeting, select key clinical studies will be covered in this overview. The target group of this review includes: neuro-oncologists, neurosurgeons, radiation oncologists and general oncologists. The research included in this review was chosen due to relevance to the target audience. This involved subjectivity on the part of the authors, and all key work was unable to be included.

Advances in primary brain tumors: phase III trials

Two late-stage clinical trials were presented that did not meet the primary endpoints. In Grupo Espanol de Investigacion en Neurooncologia (GEINO) 1401, the optimal number of adjuvant temozolomide cycles for patients with newly diagnosed glioblastoma was prospectively investigated [1]. Prior retrospective meta-analyses had suggested that there was no enhanced survival benefit for treating patients with more than six temozolomide cycles [2]; however, this had not been determined in a prospective, randomized fashion. GEINO 1401 enrolled 159 newly diagnosed nonprogressive glioblastoma subjects who had completed standard of care radiation with concurrent temozolomide [3]. After six adjuvant temozolomide cycles, patients were randomized 1:1 to either observation or six additional cycles of temozolomide. Study participants were stratified by *MGMT*-methylation status and by residual measurable disease. Median overall survival (OS) was not significantly different between the two groups: 22.0 months observation versus 18.2 months additional temozolomide, HR of 0.957 (95% CI: 0.806–1.136; p = 0.615). Two-year survival rates were also not different: 62% for the observation group versus 61% for the additional temozolomide group. *MGMT* methylation favorably influenced outcomes, whereas *IDH* mutational

status and residual disease did not. This aligns with traditional dogma, which finds that patients with glioblastoma containing a methylated *MGMT* promoter benefit from temozolamide [4].

The phase III trial EORTC 1709/CCTG CE.8 examined the effectiveness of the proteasome inhibitor marizomib in combination with standard of care for treatment of newly diagnosed glioblastoma [5]. Patients (n = 749) were randomized 1:1 to either radiation with concurrent temozolomide, followed by six adjuvant cycles of temozolomide or with the addition of marizomib beginning at the start of radiation. Marizomib was selected based on preclinical data and its blood–brain barrier (BBB) penetration properties [6]. No difference in median OS was noted: 15.9 months for the control cohort versus 15.7 months for the marizomib cohort (HR: 0.99). Additionally, there was no difference in PFS between the two arms: 6.1 months control versus 6.2 months for marizomib (HR: 1.02). Adverse events (AEs) such as ataxia, hallucinations and headache were doubled in the marizomib-treated group.

Advances in primary brain tumors: phase II trials

The clinical trial that will likely change the standard of care for craniopharyngioma patients is Alliance A071601. This phase II trial (n = 36) used the combination of *BRAF* and MEK inhibitors (vemurafenib and cobimetinib, respectively) for subjects with the *BRAF V600E* mutated papillary craniopharyngioma subtype [7]. All patients underwent prior surgical resection. *BRAF* mutation was demonstrated via immunohistochemistry. This study was based on previously published work demonstrating radiographic responses targeting this pathway in this patient population [8,9] who have a very high incidence of *BRAF* mutations [10]. Patients receive oral vemurafenib twice per day for 28 days concurrently with daily oral cobimetinib for 21 days. Results from Cohort A were presented that evaluated subjects with no prior radiation (n = 16). Fifteen patients in Cohort A had evaluable volumetric data. Among these patients, 14 demonstrated a response as defined by at least a 20% decrease in volume. The single nonresponder received only 2 days of treatment, which was discontinued due to toxicity. The median tumor volume reduction in Cohort A was ~83%, and median progression-free survival (PFS) was not reached at a median follow-up of 22 months. Seventy-five percent of patients experienced grade 3 toxicity, predominantly rash. Thirteen percent of patients developed grade 4 toxicity (hyperglycemia, elevated creatine kinase). These exceptional response rates are the first such examples of response to systemic therapy in this patient population within the context of a prospective trial. Cohort B results have not yet been released but uses the same approach in patients who have progressed after radiation.

Another randomized phase II trial evaluated two dosing regimens of the anti-VEGF antibody bevacizumab (10 mg/kg intravenously [iv.] every 2 weeks [standard] vs 3 mg/kg iv. every 2 weeks [reduced]) used in combination with a fixed dose of the anti-PD-1 antibody nivolumab (240 mg iv. every 2 weeks) in patients with recurrent glioblastoma [11]. Patients with recurrent glioblastoma (n = 90) at first recurrence were randomized 1:1 and stratified by age, Karnofsky Performance Score (KPS), extent of tumor resection and *MGMT* methylation status. OS at 12 months (OS12) in the overall patient population was not significantly different. Subgroup analysis in older adult patients (>60 years old) demonstrated a better OS12 for subjects who received the standard dose bevacizumab (46.2 vs. 23.8%) and median OS (10.6 vs 5.9 months; p = 0.046). Grade 3/4 toxicities were as anticipated. A prior phase II study has shown that there is no therapeutic benefit of the addition of anti-VEGF therapy to PD-1 blockade in recurrent glioblastoma [12]. The current study clarifies that the dosing of the bevacizumab (high dose vs low dose) does not influence outcome in combination with anti-PD-1.

On the basis of preclinical studies of sensitivity to PARP inhibition in *IDH*-mutated gliomas, a phase II clinical trial of olaparib was evaluated in recurrent *IDH*-mutant high-grade glioma (OLAGLI) patients (n = 35 total; oligodendroglioma n = 16; astrocytoma n = 14) [13–15]. The treatment was well tolerated, but median PFS was only 2 months. Six-month PFS (PFS6) was 31% with a median duration of response of 9 months (4–18+ months). Median OS (mOS) was 15.9 months, supporting potential benefit of this approach despite unremarkable outcomes based on radiographic endpoints. It is possible that the use of PARP inhibition may have greater value when used in conjunction with other therapies such as DNA-damaging agents. Potential benefit may also be more pronounced if used earlier in the treatment course as has been the case with other treatments for high-grade gliomas.

In a study evaluating the newly emerging technology of BBB disruption, a phase I/IIa study evaluated an implantable ultrasound device in patients with recurrent glioblastoma treated with carboplatin [16]. During the dose escalation phase (n = 9), the chemotherapy dose was fixed, and the number of sonications (n = 3, 6 or 9) was escalated with no dose-limiting toxicities detected. The expansion cohort of an additional 12 subjects treated with nine sonications proved tolerable with one grade 3 wound-related toxicity. Postprocedural MRI demonstrated clear

evidence of successful BBB disruption. Other systemic therapies and immunotherapies in conjunction with this approach are currently being considered for clinical trials [17–19].

Advances in primary brain tumors: phase I trials

In the domain of adoptive immunotherapy, a phase I trial examined the safety profile of autologous yδ T cells administered intracranially via a Rickham catheter (placed intracavitarily) in addition to standard radiation and chemotherapy in patients with newly diagnosed glioblastoma [20]. yδ T cells are rare immune cells that possess both innate and adaptive immune properties. Among the six patients at dose level 1, all were *IDH* wildtype, and five were *MGMT* unmethylated. One patient was unable to generate an adequate amount of yδ T cells – a potential limitation of this type of approach. Toxicities were manageable with only one patient experiencing grade 3 adverse events. Serum TNFα remained elevated through day 30 and beyond. This type of approach appears to be feasible and well tolerated thus far. Additional correlative study results with dose escalation will be of interest.

Advances in primary brain tumors: case series

A multi-institutional case series of *H3K27M* diffuse gliomas were treated with the highly selective dopamine D2 receptor antagonist ONC201 was presented [21]. Partial responses (not centrally reviewed) in two of seven patients raises interest for this type of approach especially in a patient population with limited treatment options. As proof of concept has been demonstrated in only a small number of patients [22], studies such as this help lend further support. Prospective trials (Clinicaltrials.gov: NCT03295396, NCT03416530 and NCT02525692) using this approach are ongoing.

Advances in primary brain tumors: trials in progress

We highlight two ongoing clinical trials in which preliminary results are eagerly awaited. PVSRIPO (recombinant oncolytic poliovirus) and Pembrolizumab in Patients with Recurrent Glioblastoma (LUMINOS-101) is an ongoing phase II trial for recurrent glioblastoma [23]. The previous phase I trial of PVSRIPO as monotherapy demonstrated safety and tolerability [24]. A number of key inclusion and exclusion criteria (enhancing tumor size between 1 and 5.5 cm; exclusion of high-dose steroids, notable midline-crossing tumor or extensive subependymal involvement) will need to be considered when interpreting the generalizability of the study results when available.

The second is a phase I/II study of the exportin-1 inhibitor selinexor for newly diagnosed or recurrent glioblastoma in combination with current standard of care [21]. Blocking the transport of specific proteins out of the tumor cell nucleus into the cytoplasm has long been an attractive target for the treatment of cancer [25]. In the ongoing study, newly diagnosed glioblastoma patients all receive selinexor, and the *MGMT*-methylated glioblastoma patients also receive radiation and temozolomide. The *MGMT* unmethylated subjects are treated with radiation but not the temozlomide.

Advances in CNS metastatic tumors: CSF biomarkers

Our discussion of advances for CNS metastases is focused on the exciting work in the realm of CSF biomarkers. A retrospective single-institution study was conducted evaluating CSF circulating tumor cells (CTCs) as a predictive biomarker of benefit from proton craniospinal irradiation (CSI) for leptomeningeal metastases [26]. The patient composition consisted of both lung (47%) and breast (38%) brain metastasis. Median OS was 8 months with mPFS of 6 months, notably better than accepted historical comparisons, potentially due to selection bias. Low baseline CSF CTCs were associated with a longer mOS, suggesting that this can be used as a biomarker to select which patients should be offered more aggressive treatment strategies. It remains unclear, for now, as to how CSF CTCs may guide on-treatment management of leptomeningeal metastases.

Another study evaluating CSF biomarkers examined circulating tumor DNA (ctDNA) in patients with triple-negative breast cancer (TNBC) to evaluate their risk for the development of brain metastases [27]. Patients CSF was analyzed for ctDNA after treatment with neoadjuvant chemotherapy. Thirty-nine percent of patients with TNBC who underwent neoadjuvant chemotherapy were positive for ctDNA. Among these, 98.4% developed radiographically evident brain metastases. Of the patients who were negative for CSF-ctDNA after treatment (61%), the overwhelming majority (99%) did not develop brain metastases during the course of the study. Findings from this study indicate that for patients with TNBC, positive CSF-ctDNA levels are associated with a higher risk of recurrent brain metastases, poorer OS and poorer recurrence-free survival. Accordingly, this could influence

screening protocols and open up the possibility of prophylactic approaches to prevent brain metastases for this patient population in the future.

Conclusion

Several new developments are underway for the treatment of primary CNS tumors and for the use of CSF biomarkers in CNS metastases. Results from phase III trials for glioblastoma, including GEINO 1401 and EORTC 1709/CCTG CE.8, do not alter the standard of care but do help inform our understanding of the management of this disease and future directions for investigation in the newly diagnosed setting. A nonrandomized phase II trial of *BRAF* + MEK inhibitors in papillary *BRAF V600E* craniopharyngioma, on the other hand, demonstrated excellent response rates in treatment-naive patients, influencing our therapeutic paradigm in these rare tumors. Studies of CSF CTCs and CSF ctDNA help lay the groundwork for CSF studies and potentially important prognostic and predictive biomarkers for CNS metastatic disease.

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