Society for Neuro-Oncology 2014 annual meeting updates on central nervous system metastases

Rimas V. Lukas, Minesh P. Mehta, and Maciej S. Lesniak

Department of Neurology, University of Chicago, Chicago, Illinois (R.V.L.); Section of Neurosurgery, University of Chicago, Chicago, Illinois (M.S.L.); Department of Radiation Oncology, University of Maryland, Baltimore, Maryland (M.P.M.)

Corresponding Author: Rimas V. Lukas, 5841 S. Maryland Avenue, MC 2030, Chicago, IL 60637 (rlukas@neurology.bsd.uchicago.edu).

Introduction. The 19th Annual Meeting of the Society for Neuro-Oncology (SNO) took place in November of 2014. The focus of many abstracts, as well as the Education Day, was on recent advances in the study of central nervous system (CNS) metastases.

Tumor Biology. Key studies evaluating the factors in tumors and their microenvironment associated with the development and growth of brain metastases are reviewed.

Prognostication. Studies investigating the factors that independently influence survival in participants with brain metastases are presented.

Response Assessment. The Response Assessment for Neuro-Oncology criteria for brain metastases (RANO-BM) and the Neurological Assessment in Neuro-Oncology (NANO) criteria, which were both presented, are recapped.

Radiotherapy. Studies are reviewed evaluating factors that influence survival outcomes in participants with brain metastases who were treated with radiotherapy. Studies investigating the potential risk of radiation necrosis with the combination of radiotherapy and immunotherapies are presented.

Systemic Therapies. Brain metastases-focused subset analyses from the ASCEND-1 trial for ALK-translocated non–small cell lung cancer are presented. Preclinical and clinical work on solid tumor leptomeningeal carcinomatosis is also covered.

Sequela of Central Nervous System Metastases and Their Treatments. An overview is provided of treatment-related toxicities as well as important concepts that may influence strategies to protect against these toxicities.

Conclusions. Key concepts regarding tumor biology, prognostication, response assessment, therapeutic management, and sequelae of treatment for CNS metastases are summarized. Advances in our understanding of the basic and clinical science of CNS metastases have the potential to improve outcomes for patients.

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are associated with the development and growth of brain metastases. Three key findings were (i) the clarification of our understanding of the clonal nature of brain metastases, (ii) elucidation of the specific genetic and epigenetic changes noted in and potentially driving brain metastases, and (iii) an explanation of a potentially important mechanism of the brain metastasis-tumor microenvironment that could potentially affect survival in patients with brain metastases. The first of these findings was work presented by Dr. Priscilla Brastianos (Massachusetts General Hospital) et al, for which they received the Adult Translational Research Award. They demonstrated that every brain metastasis arose from a single clone in 101 matched samples of primary tumors, brain metastases, and normal tissue samples. However, divergent evolution with respect to development of additional mutations was seen between the primary tumor and the metastases, implying that the primary tumor itself does not readily metastasize to the brain without significant mutational change. This was most pronounced in samples from lung cancer and melanoma. Evidence of convergent mutations in some cases was noted as well. Of potential therapeutic interest was the presence of actionable mutations in some of the brain metastases specimens, which were not detected in the primary tumors. These findings have the potential to influence future therapeutic strategies, especially because many mutation-specific targeted agents have blood-brain-barrier (BBB) penetrability as well as possible synergistic effect with radiation therapy.

The second key finding in brain metastases tumor biology presented at SNO addressed the differential expression of specific genes as a prerequisite for developing the capacity to metastasize to the brain. Two of these studies in breast cancer supported differential expression of genes between matched primary and brain/dural metastases, suggesting first that the “native” tumor itself does not possess the ability to metastasize to the brain and, second, that it must activate potential drivers such as STAT3, BOC, and MAP2 in order to develop such an ability. A study of epigenetic drivers for brain metastases from breast cancer reported that methylation of a set of specific genes was noted: CCDC8 (87%), BNC1 (73%), L3MBTL1 (67%), GALNT9 (53%). Downregulation of these genes using RNA interference supported potential roles in migration (CCDC8, GALNT9, BNC1, L3MBTL1) and invasion (BNC1, L3MBTL1), at least in in-vitro studies.

The third key finding regarding tumor biology in brain metastases dealt with interactions between the tumor and its microenvironment. One very interesting study using an in vitro co-culture model demonstrated potential cross-talk between stromal astrocytes and metastatic breast cancer cells via microRNAs. It would appear that reactive astrocytes are capable of transferring genetic material directly to the metastatic breast cancer cells. The acquisition of these microRNAs protected tumor cells against apoptosis, while knockdown of these induced apoptosis. This supported the authors’ provocative hypothesis that metastatic breast cancer cells are able to harness the antiapoptotic potential of the tumor microenvironment to promote survival of the brain metastases.

**Prognostication**

A number of abstracts dealt with prognosis in patients with brain metastases, highlighting the importance of a clear understanding of the natural history of disease and in turn the effects of therapeutic interventions. Results of a large, retrospective, single-institution study proposed modification of the current disease-specific graded prognostic assessment (DS-GPA). Using multivariate analysis, a number of histology-specific factors not present in the current DS-GPA system were found to correlate with overall survival (OS). A key aspect of all histologies studied was the status of extra-CNS disease. For breast cancer, these factors were the number of extracranial metastases, controlled primary, brain metastases location, and presence of leptomeningeal disease. For non-small cell lung cancer (NSCLC), the number of extracranial metastases, controlled primary, histology, hemorrhagic metastases, and sex correlated with OS. For small cell lung cancer, it was the number of extracranial metastases and controlled primary. For renal cancer, it was controlled primary and brain metastases-free interval. In melanoma, the number of extracranial metastases and age were factors in OS. BRAF mutational status was not found to be a factor in OS, although the study was not powered to look specifically at this aspect.

**Response Assessment**

The need for a unified method to assess both clinical and radiographic response across brain metastases clinical trials is acknowledged by the neuro-oncology community. Much like the recent radiographic Response Assessment for Neuro-Oncology (RANO) criteria for gliomas, an analogous set of criteria for brain metastases (RANO-BM) has been developed. A clinical assessment tool for both primary and metastatic CNS tumors, the Neurological Assessment in Neuro-Oncology (NANO), is also in development. Details of these assessment criteria were presented at the RANO Town-Hall Clinical Trial Endpoints session by Dr. Nancy Lin (Dana-Farber Cancer Institute). The new RANO-BM criteria are designed to be applicable to assessments of both local and systemic treatments. They provide bicompartamental criteria to allow for evaluation of CNS and extra-CNS effects of treatments. As we discussed earlier, the biology of the disease differs in the intra- and extra-CNS compartments, and the status of extra-CNS disease correlates with survival across most histologies. In turn, it may be expected that therapeutic interventions that may be beneficial in one compartment may not necessarily be effective in the other. The new RANO-BM will help delineate compartmental efficacy in brain metastases clinical trials. While the RANO-BM will rely on 1-dimensional measurements of up to 5 target lesions in the CNS, volumetric measurements will be encouraged as a secondary endpoint. This differs from the RANO criteria for gliomas, which employ measurements of cross-sectional area. Ideally, the new criteria will prove easy to use by clinicians and investigators. The goal of the NANO working group is the development of a similarly easy-to-use standardized tool for the neurological functioning of participants in clinical trials. It is being designed to be easily administered by investigators from a variety of subspecialty backgrounds.

**Radiotherapy**

Research presented on radiotherapy focused on whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). The majority of the work presented focused on prognostication and
prediction of response to treatment. The tone was set by an interesting study demonstrating the inadequacy of the traditional Graded Prognostic Assessment (GPA) system in the modern era. Substantial differences were seen in the observed versus predicted survival of participants with brain metastases who were treated with either SRS or WBRT in a retrospective, single-institution study of patients treated between 2006–2012. An improved understanding of prognosis is essential for interpreting results appropriately in current and future therapeutic clinical trials for this patient population. The studies described below attempt to deepen our understanding of the factors that influence prognosis for these patients.

A large retrospective study employing an investigational cohort and a separate validation cohort found that age, Karnofsky Performance Status (KPS), systemic cancer status, tumor histology, number of metastases, and tumor volume were independently associated with OS on multivariate analysis. Another smaller retrospective study, which looked at a select subset of patients with lung or melanoma primaries who had undergone resection and SRS, suggested that tumor volume, as opposed to absolute number of brain metastases, impacted OS. In one large retrospective, single-institution study, the addition of WBRT to SRS was associated with improved OS. While improved local control has been seen, improved OS has not been demonstrated previously in prospective trials. However, those prior studies were all of very limited size and were therefore not powered for survival as an endpoint. In the current study, the effect of adding WBRT to SRS appeared more pronounced in participants with ≥4 brain metastases. In this same study, the benefit of neurosurgical resection in addition to SRS was more pronounced in participants with ≤3 brain metastases. Another large retrospective, single-institution study found that KPS, presence of extracranial metastases, number, and size of brain metastases, and prior surgery independently influenced the risk of short-term (defined as ≤90 days) mortality. A prognostic model with 4 categories was developed to gauge the potential for early mortality after SRS. This model utilizes a total score for each participant, which places the participant within one of 4 prognostic groups. The total score is derived from the summation of weighted scores for each significant factor from the multivariate analysis.

One interesting randomized trial of SRS demonstrated similar outcomes in a number of parameters for participants treated with a 1-mm uniform expansion of gross tumor volume compared with a 3-mm expansion. Due to the potential for radiation necrosis, the authors argued in favor of the smaller expansion since outcomes were similar. Three retrospective studies looking at radiotherapy and systemic therapies found that the risk of acute radiation effect and radiation necrosis was increased in participants who were treated with immune checkpoint inhibitors (ICIs). ICIs are currently standard of care in tumors such as melanoma that are often treated with SRS in the context of brain metastases. This will be an important issue to consider both in routine patient care as well the design and interpretation of clinical trials for these patient populations.

**Systemic Therapies**

Of particular interest was a subset analysis of the phase I ASCEND-1 trial, which demonstrated benefit of the ALK inhibitor ceritinib (LDK378) in the treatment of NSCLC. One hundred and twenty-four of the 246 participants in the trial had brain metastases at baseline. In the small (n = 14) subset of participants with measurable brain lesions, half had measurable responses in the brain and another 20% had stable intracranial disease. This is similar to the overall extracranial response rate. This high response rate suggests BBB penetrability and the potential to use such therapies in a combinatorial manner with focal radiotherapeutic approaches. The underlying concept that such BBB-penetrating targeted agents will effectively eliminate microscopic tumor foci in the brain, whereas focally ablative therapies such as SRS will control or eradicate macroscopically visible tumors, resulting in enhanced whole brain compartmental control, without whole brain radiotherapy, is an attractive and testable hypothesis. Median progression-free survival was 6.9 months in the participants who were previously treated with an ALK inhibitor and 8.3 months in the ALK-inhibitor-naïve participants. Optimizing management in ALK-translocated NSCLC patients with brain metastases (and for that matter almost all patients with brain metastases) is of importance because the economic costs have been shown to increase substantially with the development of brain metastases. Preclinical work using a mouse xenograft model of NSCLC brain metastases demonstrated the benefit of a novel MEK inhibitor, PD032591. This opens the potential for additional therapeutic targets in this patient population.

Among the abstracts on leptomeningeal carcinomatosis was a report on clinical improvement in a breast cancer patient with a third-line bevacizumab–containing regimen. This regimen is currently being investigated in ongoing clinical trials (NCT00924820, NCT01281696). What may hold the greatest hope therapeutically will be a clearer understanding of the processes that allow extra-CNS tumors to spread to the cerebrospinal fluid and progress quickly from there. Work by Boire et al is a step in this direction. Their analysis of human and mouse cancer cell lines selected for leptomeningeal spread demonstrated unique gene expression profiles. These mouse models may be integral to preclinical studies of novel therapeutics.

**Sequelaes of CNS Metastases and Their Treatments**

The neurocognitive sequelae of CNS metastases and their treatments and the impact they have on quality of life (QOL) was addressed in a series of lectures on the Education Day by Michelle Monje-Deisseroth (Stanford), Jeffrey Wefel (MD Anderson), Lisa DeAngelis (Memorial Sloan-Kettering) and Eudocia Quant Lee (Dana-Farber Cancer Institute). Dr. Deisseroth set the stage with her discussion of the role of neurogenesis and gliogenesis in postnatal brain development. The role of neuroanatomic location, as well as the microenvironment, was detailed. Structural and functional changes are known to occur in the hippocampus after radiotherapy. In animal models, near ablation of newborn neurons with relative stability of glial cells and neural stem cells is seen. However, there is a decrease in the growth potential of the neural stem cells due to microenvironmental failure. This microenvironmental failure is thought to be due to inflammation that can be protected with indomethacin in animal models, raising the potential for its further evaluation as a protective agent. The effects of chemotherapy were noted, particularly on sensitive
oligodendrogiol precursor cells in humans as well as in animal models. Conversely, animal and human studies supporting myelin plasticity driven by physical/cognitive activity were also cited.24,25 This lends support for further investigation into aerobic exercise, cognitive training, and social skills training as regenerative therapies for CNS injury due to metastases, systemic therapies, and radiotherapy.

Dr. Wefel discussed the neurocognitive outcomes and health-related QOL endpoints from a number of key clinical trials. Of interest was support for the volume of brain metastases, rather than the absolute number, being of greater importance in cognitive symptomatology. The cognitive declines, followed by a subsequent decline in QOL noted in association with WBRT, were revisited.26–28 Dr. DeAngelis focused primarily on late toxicities of radiotherapy including radionecrosis, stroke, intracranial hemorrhage, radiation-induced tumors, and SMART syndrome (Stroke-like Migraine Attacks after Radiation Therapy). Of particular interest was the discussion of SMART syndrome, which is typically a very delayed (∼20 years) complication that may be associated with larger radiation field sizes. Radiographically focal swelling, increased signal on FLAIR, and “speckly enhancement” are seen on postcontrast studies. These findings often resolve in a few months. Finally, Dr. Lee covered the neurological complications of 2 agents: bevacizumab and ipilimumab. The rare complications of posterior reversible encephalopathy syndrome and optic neuritis were described.29,30

**Conclusions**

Greater understanding is developing about the underlying biology of CNS metastases. This understanding dovetails with a more nuanced appreciation of the natural history and radiographic manifestations of the disease. These key points have the potential to lead to important therapeutic advances. They will also allow us to better design and interpret the results of clinical trials in which these potential advances will be tested.

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**References**


