Neuro-Oncology Advances
2(1), 1–4, 2020 | doi:10.1093/noajnl/vdaa036 | Advance Access date 28 January 2020

Highlights of the 2019 Society for Neuro-Oncology Inaugural Brain Metastases Conference: establishing a dedicated meeting to address an unmet need in the field

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Abstract

Brain metastases comprise the majority of central nervous tumors in adults and confer poorer survival for patients with primary cancer. Systemic disease control is improving with advances in treatment for primary tumors and the complexity of brain metastases management is increasing with multimodality approaches incorporating combinations of surgery, radiotherapy, chemotherapy, targeted therapies, and immunotherapy. Accordingly, the Society for Neuro-Oncology established an annual brain metastases conference to unite colleagues from multiple disciplines with content spanning a range of timely topics relevant to improving our understanding of brain metastases and how they are optimally treated. The inaugural meeting on August 16–17, 2019 was very successful with 163 impactful presentations being delivered to a large multidisciplinary audience on current research advances in the field of neuro-oncology. This review summarizes the major themes of the meeting and highlights the main findings presented.

Overview

Brain metastases from extracranial primaries are the most common adult central nervous system (CNS) tumor and they confer poorer survival for primary cancer patients. The majority of brain metastases are secondary to lung cancer, breast cancer, and melanoma lesions with corresponding incidence proportions being 20–25%, 5%, and 7%, respectively, although rates are increasing with improved systemic disease control.[1–3] Standard treatment approaches include surgical resection, stereotactic radiotherapy (SRS), whole-brain radiotherapy (WBRT), chemotherapy, targeted therapies, and immunotherapy. With a mounting body of evidence regarding the benefits and limitations associated with each modality, the management of brain metastases has become increasingly complex. Multimodality personalized approaches are providing the most optimal outcomes with care being delivered by multidisciplinary teams comprised of Neurosurgeons, Neuro-Oncologists, Radiation Oncologists, and Medical Oncologists. It is timely to have a dedicated scientific meeting that provides a forum to educate and update colleagues on treatment strategies, guidelines, and research advances that improve our understanding of the biology of brain metastases as well as the treatment of patients with them.

Meeting Highlights

Recognizing this area of unmet need, the Society for Neuro-Oncology established the SNO Brain Metastases Conference, with the inaugural meeting occurring on August 16–17, 2019 in New York City, NY. The meeting was very well attended with 288

attendees representing 16 countries. The number of abstracts with emerging research selected for presentation across the 2-day conference was 151, with 33 oral presentations and 118 traditional posters. In addition, there were 12 invited talks from speakers with internationally recognized research/clinical brain metastasis expertise. Of all 118 posters presented, 35 involved radiation therapy, 17 were categorized as basic science work, 13 discussed multimodality treatment approaches, 13 focused on medical therapy, 12 were related to surgical treatment, 8 focused on leptomeningeal disease, 7 discussed clinical trials, and there were 13 additional posters on other topics of interest.

Generously supported by the Robert and Andree Rheaume Fitzhenry Brain Metastases Fund at the Princess Margaret Cancer Foundation, Dr Paul Brown gave the Fitzhenry Family Keynote Address. His talk focused on memantine and hippocampal-sparing WBRT, combining strategies to minimize neurocognitive impact from radiation as a classic model of bench-to-bedside development. Meeting co-chairs (M.S.A, A.A.A., and E.Q.L.) acknowledged the rich environment of multidisciplinary scientists covering a broad range of emerging brain metastasis research. The opening plenary session was delivered by P.Y.W. who updated the audience regarding key messages from the Food and Drug Administration (FDA) National Brain Tumor Society Brain Metastases Workshop held March 22, 2019, regarding product development for CNS metastases. Main themes covered were the need to include brain metastasis and leptomeningeal disease patients in cancer trials and to design brain metastasis specific trials, to standardize tumor response criteria across trials using the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, and to optimize endpoints for brain metastasis patients in trials. Dr Joohee Sul from the FDA was also invited to provide the regulatory perspective on these issues for product development with a focus on clinically meaningful endpoints.

Drs Ralph DeVitto, Nicole Willmarth, and M.S.A. were invited speakers from the American Brain Tumor Association and they presented initial results from a survey of physicians treating brain metastases showing treatment decision differences based on the level of experience and involvement in academia as well as a greater need for funding for brain metastasis research. G.Z. organized an Illumina sponsored a symposium regarding the application of molecular pathology to manage brain metastases with a discussion of patient cases highlighting such impacts. An additional session sponsored by Brainlab discussed technological advances in the treatment planning and delivery for brain metastases.

This review highlights the salient topics presented at the meeting with the main themes including advances with radiotherapy and systemic therapy for brain metastases, multimodality approaches to therapy, the management of leptomeningeal disease, statistical models that predict patient outcomes, basic science work and experimental brain metastasis models, and novel techniques for the imaging evaluation of brain metastases.

Radiotherapy for Brain Metastases

This very informative session provided updates on the use of hippocampal-sparing WBRT, considerations for adjuvant systemic and immune therapies after SRS, and an approach to guide salvage therapy choices at recurrence after SRS which may optimize treatment and improve patient outcomes.

Dr Wolfgang Tomé presented results from a randomized trial comparing conventional WBRT to hippocampal-sparing WBRT in 518 patients with brain metastases receiving memantine (NRG CC001). The authors demonstrated that hippocampal-sparing WBRT plus memantine (N = 257) yielded improved neurocognitive function relative to conventional WBRT plus memantine (N = 261), driven by a lower risk of deterioration in executive function at 4 months and encoding/consolidation at 6 months (hazard ratio [HR] 0.74, P = .02). These results suggest the superiority of hippocampal-sparing WBRT as opposed to conventional WBRT although further research is required to delineate whether partial hippocampal-sparing techniques should be applied to patients with metastases in or near the hippocampus. Dr Joseph Bovi then presented a secondary analysis of RTOG 0933 data, suggesting that white matter injury identified by FLAIR signal on MRI predicts cognitive decline after hippocampal-sparing WBRT in terms of recognition memory and delayed recall performance.

One of the authors (A.A.A.) presented retrospective data examining the optimal timing of systemic therapy administration relative to brain-directed SRS and subsequent development of radiation necrosis in 429 patients receiving SRS for brain metastases. The authors identified an association between receiving any systemic therapy within 5 days of SRS and subsequent development of radiation necrosis (HR 3.74, 95% CI 1.08–12.98, P = .04). If validated, these results may provide insight regarding how long systemic therapy should be held in patients with brain metastases receiving SRS. Dr Rebecca Ye discussed outcomes in 123 melanoma brain metastases treated with SRS and presented results showing that BRAF-mutated patients receiving a BRAF-targeted treatment experienced longer overall survival than all others either without a BRAF mutation or with a mutation but not receiving an inhibitor (20.5 vs 8.4 months, P = .045). She also showed that both SRS and immune checkpoint inhibitor treatments improve local intracranial disease control to similar degrees. Brain metastasis velocity, defined as the number of new lesions over time since SRS, was identified as a predictor of outcomes after SRS. This measure was presented by Michael LeCompte and may be an important consideration to guide salvage therapy decisions after SRS for brain metastases.

Systemic Therapy for Brain Metastases

The audience was delivered a comprehensive summary of systemic treatments for brain metastases, including targeted and immune therapies, which are either used currently, being studied in clinical trials, or show promise in preclinical models.

An invited talk was delivered by Dr Kim Margolin regarding the landscape of melanoma brain metastasis management, including trials showing improved intracranial response rates using multiple immune checkpoint inhibitors and multiple BRAF inhibitors compared to single-drug approaches. Dr Nancy Lin was invited to present on recent advances and ongoing trials of systemic therapy for breast cancer

brain metastases. She discussed early-phase trials showing promise using novel treatment approaches combining current HER2 inhibitors or monoclonal antibodies, cyclin-dependent kinase inhibition, and chemotherapeutic agents. Dr Harriett Kluger gave an invited talk on immunotherapies for brain metastases and approaches to managing their CNS toxicities.

Dr Jeffrey Bacha discussed a novel irreversible tyrosine kinase inhibitor (TKI), EO1001, with many advantages over existing TKIs in preclinical in vivo models. He showed data suggesting that this drug has great potency, CNS penetration, and antitumor activity compared to other TKIs including osimertinib with no observed toxicities. Based on these promising results, early-phase clinical trials are being planned. Another preclinical study was presented by Dr Martina Ott, showing that STAT3 inhibition combined with WBRT induces an immune response within the tumor microenvironment and improves survival in a rodent model. Dr Carey Anders presented results from 10 patients with active-treated breast cancer brain metastases who received liposomal irinotecan within the NCT01770353 phase 1 trial. Of these 10 patients, 3 achieved a partial intracranial response and 3 experienced intracranial stability, with 1 of these patients maintaining their response for 2 years. Finally, Dr Michelle Kim discussed the use of dinitroazetidine within an ongoing phase I/II study as a radiosensitizer for use with WBRT.

Multimodality Therapy for Brain Metastases

This session highlighted the multidisciplinary nature of brain metastasis management, with a discussion of the roles of neurosurgery, radiotherapy including neoadjuvant and adjuvant treatment, immunotherapy, and laser interstitial thermal therapy, along with approaches to predict and evaluate response to therapy.

Dr Minesh Mehta was invited to speak about the nuances of designing brain metastasis trials involving radiotherapy, including a detailed discussion on outcome selection. Another invited talk was given by Dr Veronica Chiang regarding the role for neurosurgical management in brain metastases, including diagnosis and decompression initially and after regrowth.

Dr Kailin Yang presented results from a phase I/II dose-escalation study of 27 patients managed with neoadjuvant SRS for brain metastases. Five 2–3 cm lesions were given either 18 or 21 Gy; thirteen >3 to 4 cm brain metastases received 15, 18, or 21 Gy; and eight >4 to 5 cm lesions were treated with 12 or 15 Gy. No dose-limiting toxicities occurred, providing an early indication of the potential viability of neoadjuvant SRS for patients with larger brain metastases but a longer follow-up to assess for long-term toxicities like radiation necrosis is needed. Dr Adam Lauko presented results in non-small-cell lung cancer brain metastases showing that upfront steroid treatment and a high neutrophil to lymphocyte ratio both confer poorer overall survival in the context of immune checkpoint inhibitor treatment. Dr Alexandra Giantini Larsen then presented national results of peri-operative considerations for brain metastasis surgery showing that preoperative comorbidities and infratentorial tumor location predict higher postoperative complication rates. The use of laser interstitial thermal therapy for brain metastases was presented by Dr Dhiego Bastos, discussing increased recurrence after incomplete ablation, increased ablation success for radionecrosis versus tumor, and reduced recurrence with systemic therapy added after laser therapy. Dr Michael Weller presented response assessment criteria after SRS and/or immunotherapy for melanoma brain metastases and discussed the need for standardized and validated criteria. Finally, Dr Philipp Lohmann described the use of static O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET/MRI radiomics to differentiate radiation necrosis from tumor recurrence. He showed a diagnostic accuracy of 89% in differentiating recurrence from radiation necrosis in 52 patients.

Managing Leptomeningeal Disease

The development of leptomeningeal disease in patients with cancer is very challenging to diagnose with clear management options lacking and so it is an area that demands further clinical and research focus. In this session, attendees were updated on response criteria in clinical trials for leptomeningeal disease, early-phase trials using intrathecally delivered therapies for metastases, and assessing treatment response in preclinical leptomeningeal disease models.

Dr Adrienne Boire gave an invited presentation regarding current approaches to investigate the molecular mechanisms of leptomeningeal metastasis and detection by liquid biopsy. Dr Emilie Le Rhun was invited to discuss approaches to optimize the criteria used to determine leptomeningeal disease response in clinical trials including considerations for clinical, imaging, and CSF cytology criteria.

Subsequently, Dr Priya Kumthekar presented results from a phase I/II study showing that intrathecal trastuzumab for leptomeningeal disease in HER2+ breast cancer is feasible and improves overall survival over historical controls. Dr Barbara O'Brien presented a retrospective study using intrathecal topotecan for leptomeningeal metastases of many primary cancers showing its modest side effect profile and that patients with higher functional status at diagnosis had better overall survival. Finally, Dr Vincent Law discussed a novel method of culturing tumor cells from patient CSF to study response to treatment within in-vitro and in-vivo leptomeningeal disease models.

Medical Management and Clinical Models for Brain Metastasis Patients

Collectively, this session discussed approaches to medical management in lung cancer patients along with statistical models that predict patient outcomes in cancer. The invited speaker for this session, Dr Shirish Gadgeel, discussed systemic therapy for lung cancer brain metastasis focusing on targeted treatments and immunotherapy. Dr Adam Lauko presented results showing improved overall survival in KRAS-mutant non-small-cell lung cancer with immunotherapy over chemotherapy. J.A.Z. showed results of a genome-wide DNA methylation-based model that predicts brain metastasis development from lung adenocarcinomas. The model was internally validated in an independent testing

cohort and its predictive power was independent of the components of the cancer stage in a multivariate analysis. Finally, Dr Fabian Wolpert presented a clinical model that predicts risk for venous thromboembolism in brain metastasis patients.

Basic Science Content

Overall, both tumor-specific and tumor microenvironment-related factors involved in the metastatic process were discussed along with approaches to exploit this information in order to identify cancer biomarkers and novel treatments.

Dr Patricia Steeg was an invited speaker for this session and presented preclinical data regarding brain metastasis prevention and treatment along with considerations related to the blood–tumor barrier and drug CNS penetration. Dr Jing Li also gave an invited presentation focusing on the use of combined radiation and immunotherapy with the discussion of the immunosuppressive effects of radiation, the need for an intact immune system for radiation efficacy, and the improved efficacy of radiotherapy with combined immunotherapy.

The ability of tumor-specific tGLI1 transcription factor to modify the tumor microenvironment in order to mediate breast cancer brain metastasis in a mouse model was presented by Dr Sherona Sirkisoon. It was also shown to promote angiogenesis and proliferation with the brain metastasis as well as to resist the effects of radiotherapy. The identification of ketoconazole as a tGLI1-specific inhibitor that reduces brain metastasis progression in preclinical models was discussed by Dr Daniel Doheny. Dr Katie Thies discussed the role of PDGFR beta in breast cancer stroma to promote brain metastasis in a mouse model. She showed in this model that PDGFR beta is increased in breast tumor versus normal stroma, that its activation increases breast tumor growth and brain metastasis development, and that a small molecular inhibitor of PDGFR beta (crenolanib) reduces breast brain metastasis growth. Dr Pakawat Chongsathidkiet presented results using a co-stimulatory molecule to activate T cells which prevents T-cell exhaustion due to immune checkpoint activity in brain metastases. Additionally, Dr Sheila Singh presented her work identifying and genetically characterizing brain metastasis initiating cells within in vivo models along with pilot experimentation of drugs targeting this premetastatic process. Lastly, Dr Ann Marie Pendergast presented results identifying ABL-dependent signaling networks regulating lung adenocarcinoma brain metastasis along with a corresponding biomarker and therapeutic inhibitor.

Sunrise Sessions

The first sunrise session discussed the importance of experimental models in the study of emerging therapies. Dr Carey Anders discussed breast cancer preclinical models and translation to clinical trials while Dr Priscilla Brastianos presented on clinically actionable genetic alterations in brain metastasis and monitoring of tumor evolution. Concluding the first sunrise session, Dr Manuel Valiente described the brain microenvironment and the importance of astrocyte production of STAT-3 along with treatments that alter interactions between tumor and microenvironment. The second sunrise session focused on novel imaging techniques to evaluate brain metastases. Approaches to screening and diagnosis of brain metastases, along with emerging artificial intelligence tools, were presented by Dr Raymond Huang. Additionally, techniques to optimize response assessment by imaging were discussed by Dr Timothy Kaufmann and response assessment with radiomics was focused on by Dr Pallavi Tiwari.

Summary and Future Plans

Overall, the inaugural 2-day SNO Brain Metastasis Conference was very well-attended, with many presentations from experts across multiple fields and impactful work across a wide breadth of topics that are currently relevant to the brain metastases-based research and patient care. The Society for Neuro-Oncology is planning a second annual Brain Metastasis Conference on August 14–15, 2020 in Toronto, Ontario, with Drs Priscilla Brastianos, David Shultz, and Paul Kongkham as meeting co-chairs. Based on the success of the 2019 meeting it is expected that the upcoming 2020 meeting will continue to showcase novel multidisciplinary research/approaches that enhance the care for patients with brain metastases and improve our understanding of the disease.

Keywords

brain metastases | cancer | central nervous system | Society for Neuro-Oncology.

Funding

None.

Conflict of interest statement. None.

Authorship Statement Manuscript preparation and revision: J.A.Z., A.A.A., E.Q.L., M.S.A., P.J.O., A.M., P.Y.W., and G.Z.

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