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Special issue: advances in the multimodality management of brain metastases and ongoing approaches to further improve their treatment

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Brain metastases from systemic cancer are the most common type of adult intracranial tumor and patients that develop brain metastasis experience a significantly worse prognosis.[1,2] The most common systemic cancers that metastasize to the brain are carcinomas of the lung or breast and melanoma with incidence rates at the time of diagnosis of 11.8%, 0.4%, and 0.7%, which increase to 20-25%, 5%, and 7-10%, respectively, throughout the course of disease. The rates are higher at the time of diagnosis specifically in patient subsets with metastatic cancer, where 24.2%, 7.6%, and 28.2%, respectively, have developed brain metastases.[1,3,4] Multiple therapeutic modalities are available to treat brain metastases including surgical resection, radiotherapy, and systemic therapy, including increasing roles for targeted and immunotherapies.[5,6] Accordingly, multidisciplinary approaches are needed to personalize care and provide optimal patient outcomes.

In recent years we have witnessed an increase in systemic therapies for treating extracranial disease. Although historically, patients with brain metastases have been excluded from systemic cancer therapy trials, more trials are now being carried out that allow for the inclusion of patients with brain metastases, and, more importantly, additional trials are targeted specifically towards patients with brain metastases.[7] Results from these trials offer a wealth of data that can be leveraged to guide treatment decisions and management options. We have prepared a special edition with the aim of consolidating the breadth of information available on advances in the management of brain metastases, ongoing research that will drive future advances in treatment, and a roadmap for the development of future research questions. Here we provide an overview of the topics covered in this special edition.

Focal therapies for brain metastases

- Ng et al. "Surgical advances in the management of brain metastases."
- Srinivasan et al. "Laser interstitial thermal therapy for brain metastases."
- Gondi et al. "Advances in radiotherapy for brain metastases."

These three articles outline the roles for focal treatment modalities in the management of patients with intracranial metastases. *Ng et al.* outline the indications for surgical resection along with advances in neuroimaging for preoperative planning, minimally invasive techniques, the role for supramarginal resection, the utility of local brachytherapy, and current standards for use of intraoperative adjuncts. *Srinivasan et al.* then provide a focused review on the use of laser interstitial thermal therapy (LITT), focusing on its role in recurrent brain metastases and radionecrosis that occurs following stereotactic radiosurgery (SRS). Limitations and opportunities for future indications are also reviewed. *Gondi et al.* provide a contemporary review of the role of radiotherapy in

brain metastases, with focus on the evolution in the role for SRS without whole-brain radiotherapy (WBRT). They also provide the most recent evidence for the use of memantine and hippocampal-avoidance (HA) to limit WBRT-induced cognitive toxicities. Finally, they describe ongoing work assessing simultaneous integrated boost during HA-WBRT plus memantine as a novel upcoming approach to balance tumor control and patient quality of life.

Targeted therapies for brain metastases

- Steindl et al. "Precision medicine biomarkers in brain metastases: applications, discordances and obstacles."
- Wang et al. "Emergent immunotherapy approaches for brain metastases."

This subset of special issue articles introduces targeted therapy options available for treating systemic cancer patients with brain metastases. *Steindl et al.* comprehensively summarize the available evidence supporting the use of immune checkpoint inhibitors as well as targeted therapies in subsets of patients with lung cancer, breast cancer, and melanoma. This article also describes the genetic divergence that exists between a brain metastasis lesion and matched primary tumor and ongoing work clarifying the role for brain metastasis biopsies in identifying new targetable genetic alterations not found in the primary tumor. *Wang et al.* outline the existing evidence regarding the indications for and mechanisms of resistance against immunotherapy in brain metastasis patients, with a focus on melanoma and genitourinary malignancies as the two most highly studied brain metastasis types.

Multimodality brain metastasis treatment

- Myall et al. "Management of brain metastases in lung cancer: evolving roles for radiation and systemic treatment in the era of targeted and immune therapies."
- Sammons et al. "Advances in the management of breast cancer brain metastases."
- Saberian et al. "Targeted therapy strategies for melanoma brain metastasis."
- Sener et al. "Advances in the diagnosis, evaluation, and management of leptomeningeal disease."

Collectively, these articles outline the use of multiple treatment modalities in managing intracranial metastasis patients with a focus on the three most common brain metastasis types along with leptomeningeal disease. The article by *Myall et al.* describes multimodality treatment options utilized in lung cancer including targeted therapies for tumors with EGFR/ALK or other genomic alterations along with the use of chemotherapy, immunotherapy, and bevacizumab for others without a known genetic driver. *Sammons et al.* then discuss the multiple therapeutic modalities used to manage breast cancer brain metastases which includes targeted therapies for hormone receptor-positive and HER2-positive breast cancer along with chemotherapy. Ongoing work assessing the role for other systemic therapies in triple negative tumors is discussed, including agents that target DNA repair. *Saberian et al.* outline therapies available for melanomas with description of the role for BRAF/MEK and KIT inhibitors as well as their combinatorial utility together with other treatment modalities. Finally, the *Sener et al.* article summarizes improvements in the diagnosis of leptomeningeal disease as well as multimodality treatment options available including consideration for intrathecal therapy and cerebrospinal fluid diversion.

Approaches to limit therapy-induced morbidity

- Parsons et al. "Preservation of neurocognitive function in the treatment of brain metastases."
- Burton et al. "A review of neurotoxicities associated with immunotherapy and a framework for evaluation."

This section discusses treatment-related morbidities, how best to diagnose and manage them, and, ultimately, techniques/therapies utilized to prevent them. The review by *Parsons et al.* describes how multiple treatment modalities cause neurocognitive decline, provides approaches to prevent their development, and discusses how they may be optimally managed to limit impact on patient function. *Burton et al.* then comprehensively outline potential central and peripheral neurological toxicities of immune checkpoint inhibitors and chimeric antigen receptor T cell therapies. Frameworks for the diagnosis of these toxicities are provided along with a summary of consensus guidelines for their management.

Major themes in ongoing research that may impact future treatment

- Srinivasan et al. "The microenvironment of brain metastases from solid tumors."
- Blethen et al. "Modulation of the blood-tumor barrier to enhance drug delivery and efficacy for brain metastases."
- Miarka et al. "Animal models of brain metastasis."

The final article group focuses on current challenges in the treatment of brain metastases along with approaches to improve their treatment in the future, including potential novel therapies. *Srinivasan et al.* provide a review of literature describing the role of the tumor microenviroment (TME) in brain metastasis development and the impact of the TME on treatment failure. New potential treatment targets associated with mechanisms involved in the development of a brain metastasis within the TME are also discussed. *Blethen et al.* review the impact of the blood-tumor barrier in limiting the brain penetrance of many drugs and ongoing work on techniques to increase blood-tumor barrier permeability, including low intensity focused ultrasound. Finally, *Miarka et al.* summarize available animal models of brain metastasis and how they may be used to identify and evaluate novel therapies.

Conclusion

Brain metastases are associated with significant morbidity and mortality. There has been a recent increase in the inclusion of brain metastasis patients in clinical trials for systemic cancer, along with recent advances in our understanding of the biology of these tumors, which have contributed to improved patient outcomes. This special issue provides a collection of contemporary reviews highlighting what the editorial team considers to be current and relevant for this expanding field, in order to guide clinical management decisions, address gaps in knowledge, and guide ongoing and future research.

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