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Approaches for Optimal Drug Development and Clinical Trial Design for Breast Cancer Brain Metastasis

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Brain metastases arising from breast cancer constitute a clinically unmet need and a situation that portends a poor prognosis with few therapeutic options. Current treatment options are limited to local therapies including neurosurgical resection, radiation treatment (ie, stereotactic radiation surgery [SRS] and whole brain radiation therapy [WBRT]), or combinations of these. Historically, patients with breast cancer brain metastases (BCBMs) have been excluded from clinical trials or have been considered together with patients who have brain metastases from a variety of solid tumor types (ie, lung cancer, melanoma). This has resulted in less than optimal scientific evidence specific to the treatment of BCBMs. [1] Recently, the focus on management of BCBMs has intensified: clinical trials are now specifically enrolling patients with BCBMs,[2] the American Society of Clinical Oncology published its inaugural guidelines on the treatment of human epidermal growth factor receptor 2 (HER2)-positive BCBMs,[3] and the Response Assessment in Neuro-Oncology (RANO) Working Group defined standard trial design and outcome measurements specific to brain metastases.[4] However, despite these positive advances there continues to be no approved systemic therapy for BCBMs.

How can we better develop safe and effective therapeutics to improve the treatment of BCBMs? In a review in this issue of ONCOLOGY, Drs. Lim and Lin propose that “the ideal BCBM systemic therapy should specifically target ligands that are expressed by tumor cells and responsible for its tumorigenic phenotype, adequately penetrate the blood-brain barrier, effectively control extracranial disease, and be relatively well tolerated.”[5] Addressing these four key components will be critical in the development of therapies for treating patients with BCBMs, and in this commentary we share our perspective on each of these.

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(1) An understanding of the underlying biology fostering growth and survival of BCBMs is essential to identify optimal therapeutic targets and develop effective therapies

This is particularly important for patients with triple-negative breast cancer, who exhibit the highest frequency of brain metastases, and for whom there are currently no approved targeted therapies to treat metastatic, extracranial disease. Recent preclinical research demonstrates that metastatic breast cancer cells in the brain microenvironment acquire neuronal-like phenotypes unique to brain metastasis. [6] Additionally, up-regulation of γ-aminobutyric acid (GABA)-related genes in BCBMs,[7] coupled with induction of surrounding glia to differentiate and release pro-proliferative and pro-survival signals,[8,9] demonstrates the ability of breast cancer cells to adapt to and co-opt the surrounding brain microenvironment to enhance their own growth and survival. Steps to compare primary breast cancer tumors and their matched brain metastases are underway. Results have demonstrated a predilection for basal-like, HER2-enriched, and claudin-low molecular subtypes to metastasize to the brain as compared to other breast cancer subtypes.[10] Future studies identifying unique and critical molecular drivers of BCBMs could provide more precise targets for future therapeutic development.

(2) Ideal interventions for BCBMs must penetrate the blood-brain barrier (BBB)

Ideal properties of agents crossing the BBB have been previously described[11]; however, recent literature demonstrates distinct heterogeneity in the permeability or “leakiness” of the BBB at the tumor, independent of the size of the lesion.[12] A greater understanding of any resulting alterations in drug pharmacokinetics must be further studied. Lim and Lin describe a landmark study demonstrating trastuzumab accumulation in brain metastases[13] and a survival benefit with continued treatment in the setting of stable intracranial and extracranial disease.[14] Additionally, carrier-mediated agents,[15] nanoparticles,[16] and liposomal agents[17] have been shown to have preclinical activity against intracranial disease, and activity of these novel agents in patients with BCBMs has been illustrated in a retrospective study.[18] To more effectively understand the pharmacokinetics of novel therapies, a “window trial” design, in which drug is administered to patients for a short duration (ie, 7–21 days) followed by planned neurosurgical resection for clinical indications, could help address these questions. As an example, Seidman and colleagues recently reported the pharmacokinetic profile of lapatinib and capecitabine in cerebral spinal fluid, brain metastasis tissues, and blood.[19] Studies such as this one will be critical to advance our understanding of the heterogeneity of the “normal brain–brain tumor” barrier and the distribution of promising brain-penetrant treatments with the ultimate goal of correlating concentrations with outcome.

(3) Effective therapeutic strategies for BCBMs must control both extracranial (visceral) and intracranial disease

Up to 80% of breast cancer patients with brain metastasis have concurrent extracranial disease, depending on the breast cancer subtype.[20] As described by Lim and Lin, the current standard of care to treat BCBMS is grounded in local therapies (ie, radiation and neurosurgical resection).[5] Clinical trial design should incorporate both systemic and local therapies with the goal of controlling both intracranial and extracranial disease while maintaining patients' quality of life. The LANDSCAPE trial marked the first effort to evaluate systemic therapy in newly diagnosed HER2-positive patients with BCBMs prior to radiation therapy. [21] Lim and Lin comment that the LANDSCAPE treatment of lapatinib and capecitabine "represents a viable alternative first-line treatment option for patients with HER2-positive BCBMs." Finally, inclusion of patients with BCBMs in phase I trials is necessary to evaluate the role of novel systemic treatments to simultaneously control extracranial and intracranial disease.

(4) Maintenance of patients' quality of life while they are receiving novel brain-directed therapies is critical in the treatment of BCBMs

Current local therapies carry a high risk of neurocognitive injury and subsequent decline in neurocognition.[22] WBRT, while providing additional local control of intracranial disease when coupled with stereotactic radiosurgery, results in accelerated decline in neurocognition without an overall survival advantage.[23] Delaying the time to WBRT through the thoughtful use of effective systemic therapies could provide a substantial benefit in terms of quality of life. Current studies are directly investigating the impact of WBRT on neurocognitive outcomes. [24] Additionally, novel clinical trial designs employing a secondary prevention approach will evaluate promising systemic therapies following stereotactic radiosurgery in an effort to delay time to WBRT.[25] A unified evaluation of toxicities and their impact on quality of life, particularly as they relate to neurocognition, should accompany studies of therapy for BCBMs. Adherence to the RANO published guidelines to evaluate neurocognitive outcomes[24] in clinical trials of treatment for BCBMs will provide a more consistent approach for future studies in this population.

Careful research in the basic sciences and clinical realm, coupled with psychosocial evaluation of treatment side effects, is critical for improved management of BCBMs. A deeper understanding of the molecular drivers of BCBMs, the interplay of tumor cells in the brain microenvironment, and effective BBB penetration must all be considered in the development of future therapies. Effective and concurrent treatment of extracranial disease are also essential. While clinical trials have become both more inclusive and specifically designed for patients with BCBMs, we are still left without approved brain-penetrant therapeutics capable of prolonging survival for our patients while maintaining quality of life. This situation demands continued research efforts to improve the current treatment paradigm for our patients with BCBM.

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