Management of Breast Cancer Brain Metastases Is Moving Forward, but New Options Are Still Needed

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Prevention of CNS seeding early in the metastatic disease course using drugs with both intra- and extracranial activity will be crucial to improving outcomes in patients with breast cancer brain metastases.

Breast cancer brain metastases (BCBMs) are challenging, as they can occur up to several years after diagnosis and in the setting of controlled extracranial disease. Increased survival of breast cancer patients through more effective systemic treatments has unmasked a subpopulation with central nervous system (CNS) metastases, which is now one of the major clinical factors impacting quality of life and survival in metastatic breast cancer (MBC). Patients with certain molecular subtypes, such as triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, have increased risk of CNS relapse.[1-3] Efforts at further refining populations at risk—such as patients who have the basal phenotype, who were diagnosed with breast cancer at an early age, who have visceral metastases, and whose primary breast tumors carry certain gene-expression profiles—may allow screening of selected patients for early identification, treatment, and management of brain metastases. Currently recommendations do not exist for screening of occult brain metastases in these high-risk patients. In addition, it has not been consistently shown that early treatment of occult brain metastases leads to improved outcomes; it may simply produce a lead-time bias.[4]

Prevention of CNS seeding early in the metastatic disease course using drugs with both intra- and extracranial activity will be crucial to improving outcomes in patients with BCBMs. Findings from DNA-microarray studies of human primary breast carcinomas indicate that the ability to metastasize is an early and inherent property of the breast tumor. In a study by Klein et al, samples of 18 metastases to brain and 8 metastases to bone from human breast cancer were tested to identify tissue-specific metastasis genes.[5] Results showed that brain and bone metastases could be separated into distinct groups based on differential gene expression. Furthermore, the expression profile of these genes permitted accurate classification of primary breast tumors according to their metastatic sites. This finding could have therapeutic implications for potential prevention studies of adjuvant CNS-directed therapies, similar to those used in cancers like small cell lung cancer or acute lymphocytic leukemia (ALL)—if primary tumors that would ultimately metastasize to brain could be identified. Ongoing efforts with expression profiling of primary breast tumor and matched metastases may provide the opportunity to identify candidate genes as markers that predict the sites of metastases, and to tailor therapy.

While radiation therapy (RT) has been the cornerstone of treatment for brain metastases, whole-brain radiation therapy (WBRT) is not without associated toxicity, and the optimal timing of WBRT is unknown. Although local therapies such as WBRT are often given as upfront therapy, it is unknown whether it best to administer this treatment initially or reserve it for patients who do not respond to systemic chemotherapy. Patients with a low CNS burden and concurrent extracranial disease are perfect candidates for trials of systemic CNS-active chemotherapy before administration of local therapies, in an effort to delay side effects of WBRT. The feasibility of this approach was illustrated in the LANDSCAPE trial, in which upfront combination therapy with lapatinib and capecitabine, given prior to RT, yielded CNS response rates as high as 66%.[6] As newer therapies evolve, it is imperative to know their CNS efficacy. In instances in which there is suspected CNS activity based on preclinical models or mechanisms of action, as with small-molecule HER2 tyrosine kinase inhibitors, it is truly reasonable to proceed with systemic therapy in the setting of small, asymptomatic brain metastases.

As described by Drs. Lim and Lin in their timely and comprehensive review on breast cancer brain metastases in this issue of ONCOLOGY,[7] a number of challenges are breast cancer-subtype dependent. The shorter time to development of CNS metastases in TNBC, and shorter survival time...
after brain metastasis diagnosis compared with HER2-positive breast cancer, are related to the more aggressive biology of TNBC but are also due to more effective anti-HER therapies that allow for better disease control in that subgroup.[8] TNBC is a challenge with regard to both CNS and systemic control. Ideally, trials looking at TNBC brain metastases will need to involve agents believed to have high overall disease activity. Because TNBC is also a heterogeneous disease, future trial efforts should include evaluation of differential responses based on molecular subtypes. The challenges in patients with HER2-positive brain metastases are different. HER2-positive CNS disease can occur in the setting of controlled as well as uncontrolled systemic disease. The molecular size of anti-HER2 humanized monoclonal antibodies such as trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1) has historically been presumed to prevent these agents from crossing the blood-brain barrier (BBB). The bioavailability of trastuzumab remains controversial, and while evidence supports CNS permeation, this is likely limited.[9,10] Pertuzumab and T-DM1 are two newer anti-HER2 therapies approved by the US Food and Drug Administration for patients with HER2-positive disease; however prospective data on the CNS efficacy of these therapies are lacking. In clinical trials of pertuzumab, used in combination with trastuzumab and docetaxel for chemotherapy-naive MBC, patients with CNS metastases were excluded.[11] In the seminal trial of T-DM1, an antibody-drug conjugate that combines anti-HER2 properties of trastuzumab with the cytotoxic agent emtansine (DM1), patients with treated CNS metastases were allowed to enroll provided that there was at least a 2-month interval from their last CNS-directed therapy.[12] The trial did not require serial CNS imaging, however. In a retrospective exploratory analysis of data from EMILIA, a subset of patients with brain metastases at baseline on T-DM1 had significantly improved outcomes compared with patients treated with lapatinib/capecitabine, a regimen with well-described efficacy in CNS disease, similar to efficacy observed in breast cancer patients without BCBMs. The T-DM1 arm had an overall survival time of 26.8 months, compared with 12.9 months in the lapatinib/capecitabine arm.[13] These observations are encouraging and need to be confirmed in prospective trials.

The above data underscore the fact that not only molecular size but also other properties of a given drug, such as structure, lipophilicity, biodistribution, and the effect of drug efflux pumps, are important to gaining access to the brain. There is even greater complexity since (1) agents that target the tumor stroma or vasculature, such as bevacizumab, may not need to pass through the BBB in order to be effective[14,15]; (2) the integrity of the BBB is questionable itself in the presence of brain metastases[9]; and (3) drugs may have different CNS bioavailability[10] and efficacy[6,16] when used upfront for CNS metastases vs after local therapies (radiation or surgery).

The CEREBEL trial addressed the issue of primary prevention of brain metastases in HER2-positive MBC patients who had not yet developed brain metastases, comparing lapatinib plus capecitabine vs trastuzumab plus capecitabine, with development of CNS metastases as the primary endpoint.[17] Of note, patients were required to have CNS screening at baseline, which led to the exclusion of 20% of the study patients, who had asymptomatic brain metastases). Unfortunately the study results were inconclusive due to the scarcity of events in each arm (3% in the lapatinib/capecitabine arm and 5% in the trastuzumab/capecitabine arm). Importantly the trastuzumab-containing arm outperformed the lapatinib arm in terms of objective response rate, progression-free survival overall survival. Nonetheless, the important lesson learned was that systemic control remains of key importance in HER2-positive disease, and we hope that new, more effective systemic treatment early in the disease course can delay or prevent CNS metastases later. Later analyses of trials like neo-ALTTO (the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation study), ALTTO (the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation study), and National Surgical Adjuvant Breast and Bowel Project (NSABP) B41 should be reviewed to evaluate the data for development of CNS metastases, to again assess whether the brain metastases outcomes differ from outcomes of the entire population in a lapatinib- vs trastuzumab-treated population.

Efficacy of novel systemic therapies in BCBMs should be incorporated routinely into clinical trials, early in the process. Allowing for systematic collection of data on brain metastases, similar to what was done in the EMILIA trial, is important—especially in high-risk groups such as patients with TNBC and HER2-positive disease. Time to development of CNS metastases is a potential endpoint to examine when testing new therapies in the setting of advanced breast cancer. It is also essential to include patients with treated and stable brain metastases in clinical trials.[17] There are many challenges and considerations when designing trials specific to the management of BCBMs, including defining CNS response and progression criteria (modified Response Evaluation Criteria in Solid Tumors [RECIST] vs volumetric responses vs modified Revised Assessment in Neuro-Oncology [RANO] Working Group criteria), incorporation of neurocognitive and quality-of-life testing.
simultaneously measuring intra- and extracranial responses, and using accurate cross-trial comparisons. Clinical trials in patients with BCBMs should involve testing of BBB permeation using novel biomarker imaging techniques and ascertain predictors of response. As discussed by Lim and Lin in their review, there is potential for targeting specific genomic alterations, such as mutations of PIK3CA or BRCA, with novel treatments. The increasing use of breast cancer genomic analysis offers tremendous opportunities for understanding the molecular basis of breast cancer. Intracranial specimens and cerebrospinal fluid should be examined whenever feasible, to facilitate better understanding of mechanisms underlying the pathogenesis of brain metastases and to allow for assessment of treatment pharmacodynamics and pharmacokinetics. This could enable identification of targetable genomic alterations, alternative pathways implicated in drug resistance, and homing signatures associated with a predilection for the CNS. While there has been progress in local therapies for CNS metastases with the advent of stereotactic radiosurgery and increased implementation of brain metastases–specific trials, particularly in HER2-positive disease, there is still a great need for additional options for patients. With better understanding of the biology of CNS spread, and by either continuing to conduct studies specifically for breast cancer patients with CNS involvement or allowing patients with CNS metastases to be enrolled in clinical trials, we will persist in making the strides needed to limit this potentially devastating complication.

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