Brain Metastasis in Breast Cancer: Last Barrier to the Cure?


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The last two decades have seen the development of a variety of novel therapeutic agents that have improved prognoses for women with breast cancer. Certainly for women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, the introduction of trastuzumab (Herceptin) has altered the natural history of the disease, turning a once aggressive cancer into one with a favorable prognosis.[1] Moreover, our understanding of the biology of breast cancer has also grown; we have realized that it is not a homogeneous disease but rather a heterogeneous one composed of a number of subtypes, each with its own unique natural history and survival outcomes.[2] Despite such advances, however, a diagnosis of brain metastases in a woman with breast cancer still connotes a debilitating and incurable condition. This review by Elgene Lim and Nancy U. Lin is timely and takes us on a biological tour of brain metastases in women with breast cancer; against this backdrop, it comprehensively summarizes all the data currently available on the development of—and survival following—some of the newer management approaches evaluated in patients with brain metastases. Several important questions are alluded to in the review that deserve more attention, however.

Current management strategies for brain metastases do not drastically alter associated outcomes. The question, then, is whether there is a role for the prevention of brain metastases. Lim and Lin correctly point out that the subtype of the primary breast tumor influences the natural development of brain metastases. Data indicate that the highest incidences of brain metastases occur in women with HER2-positive and triple receptor-negative breast cancer (TNBC). In a recent publication, Dawood et al.[3] noted an 8% 2-year cumulative incidence of brain metastases in women with stage III TNBC. However, most women with TNBC who have brain metastases succumb as a result of progression of disease in both the CNS and concomitant distant sites, which is in contrast to women with HER2-positive disease who have brain metastases, more than half of whom die as a result of progression of disease in the CNS.[4]

From the epidemiologic data that have been published and from what is known of the course of each breast cancer subtype, it appears that prevention of brain metastases would be an option to explore among women with HER2-positive breast cancer. The next logical question would be whether all women with HER2-positive breast cancer would benefit from brain metastases-prevention strategies. Not all women with HER2-positive breast cancer develop brain metastases, and it would be necessary to accurately identify the women who are at high risk of developing this complication. At ASCO 2012, Duchnowska et al.[5] presented interesting results of a study that attempted to address these issues. The investigators developed a 13-gene signature that strongly predicted for the rapid development of brain metastases among women with advanced HER2-positive breast cancer. They reported a median brain metastases-free survival of 54 months vs 86 months ($P = .032$) among tumors that had high and low expressions of the 13-gene signature, respectively. If we were to accurately identify groups of women with HER2-positive disease who would eventually develop brain metastases, what strategy for prevention would be ideal? The long-term neurocognitive side effects typically associated with whole brain radiation therapy (WBRT) have resulted in this treatment modality being reserved for established brain metastases. A tyrosine kinase inhibitor such as lapatinib (Tykerb), which is able to cross the blood-brain barrier, would be an interesting preventive agent, but lapatinib is also associated with side effects, and the length of time required for preventive treatment might be an issue. Indeed, in a recent study, Bachelot et al.[6] demonstrated activity of the lapatinib and capcitabine combination in women with HER2-positive breast cancer and brain metastases before treatment with WBRT. The authors were able to demonstrate an overall CNS response rate of 67%. Results of prospective clinical trials incorporating lapatinib—such as the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study, which includes the
incidence of CNS metastases as a secondary end point—should be able to better define the role of this agent in the prevention setting.

Lim and Lin discuss at length management strategies for women with brain metastases and the advances seen over time in this area. However, the fact remains that the options available to oncologists treating women with brain metastases are limited; these limited options are further complicated by issues of how to incorporate CNS-targeted treatments and management of other systemic metastases while at the same time maintaining an adequate quality of life. In women with TNBC, radiation therapy and surgery remain standard of care. Several agents are being explored in prospective studies for women with HER2-negative breast cancer, including poly (ADP-ribose) polymerase (PARP) inhibitors and, interestingly, bevacizumab (Avastin). Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has been shown to have modest activity in metastatic breast cancer; nonetheless, the US Food and Drug Administration (FDA) recently withdrew its approval of bevacizumab in this setting due to lack of demonstration of an overall survival benefit. However, given the agent’s known activity in glioblastoma multiforme, it will be interesting to prospectively evaluate its activity in brain metastases from breast cancer.

In conclusion, we certainly have witnessed significant improvements in the management of breast cancer. We have moved from an era in which the development of brain metastases signified the end of the natural course of an aggressive disease and moved into one in which the development of brain metastases signifies that women are living long enough for these to develop. The incidence of brain metastases is actually rising, signifying a need for better screening, prevention, and therapeutic strategies. If we truly believe that the subtype of the primary breast tumor drives the incidence and the natural history of brain metastases, then our knowledge of the biology of the various tumor subtypes should guide research aimed at identifying therapeutic targets for each subtype of disease in both the prevention and therapeutic settings.

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References:

REFERENCES


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