BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Management of Brain Metastases in Breast Cancer

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H&O How common are brain metastases?

CA Lung cancer, melanoma, and breast cancer are the 3 types of cancers that are most likely to metastasize to the brain. Other solid-tumor cancers and some hematologic malignancies also can metastasize to the brain, but this occurs much less frequently. Brain metastases are common enough in advanced lung cancer that we order magnetic resonance imaging of the brain at initial presentation, whereas we proceed with intracranial imaging in advanced breast cancer only if patients have symptoms that are suggestive of brain metastases.

Across all subtypes, approximately 10% to 15% of women with metastatic breast cancer develop brain metastases. This rate is as high as 30% for women with advanced human epidermal growth factor receptor 2 (HER2)-positive disease, and as high as 50% for women with metastatic triple-negative breast cancer.

H&O Is the number of women living with breast cancer that has metastasized to the brain increasing?

CA We do not know for certain the answer to that question, although our Brain Metastases Specialty Clinic is working with our partners at the Dana-Farber Cancer Institute to examine how the incidence is changing over time. It is logical that the incidence of brain metastases would increase as patients live longer, thanks to medications that work outside of the brain but are unable to reach the brain. For example, trastuzumab (Herceptin, Genentech) is a big, bulky monoclonal antibody that has a difficult time permeating the blood-brain barrier but does an excellent job treating HER2-positive breast cancer elsewhere in the body.

H&O What are the sequelae of brain metastases?

CA The skull is a confined space, and any additional mass can lead to pressure on the brain and related symptoms. In our clinic, we become concerned about the possibility of brain metastases if patients begin to experience headaches, blurred vision, or unexplained nausea.

The symptoms of brain metastases are highly linked to their location. For example, patients with brain metastases in the frontal lobes tend to exhibit emotional lability and changes in personality. Patients with brain metastases in the parietal lobes tend to have difficulty with speech, movement, and sensation in the extremities. Those with brain metastases in the cerebellum can have gait disturbances and difficulty with coordination. Difficulty with vision can occur with brain metastases in the occipital lobes.

H&O What is the prognosis for patients with brain metastases?

CA Historically, a diagnosis of brain metastases conferred a life expectancy of approximately 6 months. With the addition of radiation therapy and improved systemic therapy, however, we have seen a dramatic improvement in life expectancy.

Prognosis in these patients is highly linked to breast cancer subtype. In a very well done study from Poland, Anna Niwinska and colleagues looked at 222 patients with breast cancer that had metastasized to the brain who were treated with whole-brain radiotherapy. The median survival was approximately 4 months in patients with triple-negative breast cancer, 9 months in those with HER2-positive breast cancer, and 15 months in those with luminal (hormone receptor–positive) breast cancer.

More recently, our clinic published results on 65 patients with breast cancer that had metastasized to the brain, with Megan McKee as the first author. We found that median survival across all subtypes was 2.11 years from a diagnosis of brain metastases (95% CI, 1.31-2.47), whereas those with triple-negative breast cancer lived a median of 1.15 years (95% CI, 0.4-2.43) and those with hormone receptor–positive/HER2-negative breast cancer lived a median of 1.31 years (95% CI, 0.51-2.52). Those with HER2-positive breast cancer lived a median of 3.03 years (95% CI, 1.94-not estimable); we have seen significant strides in treatment of these patients. The subtype where we have seen the least improvement is triple-negative breast cancer, although we hope to see improvements in the near future.

H&O Could you discuss the use of the diagnosis-specific Graded Prognostic Assessment (GPA) to predict survival?

CA Initially, the GPA score depended on the patient's age, the patient's performance status, and the presence or control of extracranial disease. These 3 factors were used to determine the prognosis of a particular patient. For example, a 35-year-old patient with an excellent performance status and no evidence of extracranial disease would have a better prognosis than an elderly patient with a performance status of 2 or 3 and uncontrolled lung metastases. This score helped us to tailor therapies and counsel patients on what to expect.

Since the original GPA was published, we have come to recognize that histologic subtype among patients with breast cancer also plays a role in prognosis, and the scale has been adjusted.

H&O What is the most common cause of death in patients who have breast cancer that has metastasized to the brain?

CA The answer to that depends on the status of the extracranial disease and on the histologic subtype. For example, women with HER2-positive breast cancer—who receive targeted agents that do not treat the brain—are more likely to experience a neurologic death. A woman with triple-negative breast cancer is more likely to develop metastases to both the lung and the brain, so in many cases it is uncontrolled extracranial metastases that lead to death. Of course, it can be difficult to determine—even at the patient's bedside—the precise source of a patient's decline as the disease progresses overall.

H&O How has our understanding and management of brain metastases changed over the past 5 years?

CA We are seeing advances in both local and systemic therapy. The ability of neurosurgeons to locate and resect brain metastases has improved, and radiation oncology has improved as well. Traditional radiation treatment of brain metastases involved whole-brain radiation therapy, which includes low doses of radiation to the brain over the course of approximately 10 to 15 days. This approach irradiates a large amount of normal brain in addition to the brain metastases, which can lead to a decline in neurocognition and performance status.

More recently, the use of stereotactic radiosurgery has revolutionized the care of patients with brain metastases who have a limited number of lesions—usually no more than four. With stereotactic radiosurgery, the radiation oncologist delivers beams of high-dose radiation to tumors with extreme accuracy over 1 or 2 days, so that the remainder of the brain remains untouched by radiation.

When stereotactic radiotherapy is not possible, another option is whole-brain radiation. Newer strategies spare the hippocampus, the region of the brain that is our seat of memory. We have seen some very promising clinical trial results with hippocampus-sparing whole-brain radiation to preserve neurocognitive function.

Regarding systemic therapy, we are beginning to see tremendous movement in the development of agents that can permeate the brain. Although we do not yet have any US Food and Drug Administration (FDA)–approved agents for brain metastases, many pharmaceutical companies have recognized this unmet need and are developing compounds for this patient population. Some of these compounds are molecules that are just small enough to cross the blood-brain barrier, and others are carrier-mediated systemic therapies, such as nanoparticles. Researchers, including our group, have shown that nanoparticle delivery to the brain enhances the intratumoral concentrations of different anticancer agents.

Another investigational approach is the administration of the dementia agent memantine to patients undergoing whole-brain radiation therapy in an effort to reduce the associated decline in neurocognition. In an early trial by Paul Brown and colleagues, the use of memantine led to significant improvements in time to cognitive decline, probability of cognitive function failure at 24 weeks, executive function at 8 and 16 weeks, and processing speed and delayed recognition at 24 weeks compared with placebo. There was also a statistically nonsignificant trend toward less decline in neurocognitive function.

H&O Are we getting any better at preventing brain metastases?

CA We do not have any agents that have been shown to prevent brain metastases. As we get better at treating

extracranial metastases and preventing breast cancer from entering the lymphatic system, however, the likelihood that breast cancer will reach the central nervous system decreases. We are seeing significant advances in immunotherapy and molecularly targeted therapy in both melanoma and lung cancer, so that holds true for other solid tumors as well.

H&O Is there anything else you would like to say about how quality of life is affected by treatment for brain metastases?

CA We have to strike a careful balance when we decide how much therapy to administer to patients with brain metastases. Approximately a decade ago, a study attempted to tease out which was more responsible for decline in quality of life in patients with cancer: therapies or disease. Although treatments have side effects, they often do not compromise quality of life as much as the symptoms from progressive disease. The ultimate goal is to shield our patients from the side effects of brain metastases.

H&O Could you talk more about the Brain Metastases Specialty Clinic at your institution?

CA Managing care for patients with brain metastases is very difficult, which is why we set up a coordinated, multidisciplinary clinic. These patients have issues that need to be addressed quickly by physicians in multiple specialties, including radiation oncology, neurosurgery, and medical oncology. Having the clinic means that patients do not have to wait a week for an appointment with a particular specialist, or travel throughout the hospital or to different locations to address their concerns—something that can pose a particular challenge for someone in fragile health. I would encourage other hospitals to set up similar clinics; we spelled out our approach in the piece with Megan McKee as the first author.

H&O Which clinical trials looking at patients with breast cancer that has metastasized to the brain would you like to call out?

CA Numerous trials are being carried out. The JPBO study (A Study of Abemaciclib [LY2835219] in Participants With Breast Cancer, Non-small Cell Lung Cancer, or Melanoma That Has Spread to the Brain) is looking at the use of the cyclin-dependent kinase (CDK) 4/6 inhibitor abemaciclib in patients with hormone receptor–positive breast cancer who have brain metastases (NCT02308020). The Dana-Farber Cancer Institute is enrolling patients in a study that is examining the use of neratinib and capecitabine for patients with HER2-positive breast cancer and brain metastases (NCT01494662). We are currently enrolling patients in a study at the University of North Carolina evaluating the use of everolimus (Afinitor, Novartis) in patients with HER2-positive breast cancer and brain metastases (NCT01305941). In addition, a phase 2 study that has completed accrual is investigating the use of ANG1005, which can cross the blood-brain barrier, in patients with breast cancer that has metastasized to the brain (NCT02048059). A number of exciting compounds are being investigated, and I recommend ClinicalTrials.gov and BrainMetsBC.org as valuable resources for physicians and patients. Because we do not have an FDA-approved agent for treating brain metastases, enrollment in a clinical trial is a good idea for these patients. I also think that more breast cancer trials in general should include patients with brain metastases.

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Suggested Readings

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