

BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Update on Managing Brain Metastases in Breast Cancer



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H&O How common are brain metastases in breast cancer?

NL Among women with metastatic breast cancer, up to 50% of those with human epidermal growth factor 2 (HER2)-positive disease (Figure) and approximately 25% to 40% of women with triple-negative disease have brain metastases. The rate of brain metastases is much lower in women with early-stage disease. For example, metastatic disease that presents initially in the brain develops in fewer than 2% of patients with early-stage HER2-positive breast cancer.

H&O How is prognosis determined in patients with brain metastases?

NL The most important factors are performance status and tumor subtype, but we also look at age and comorbidities. Patients with brain metastases who have HER2-positive breast cancer tend to do the best, and those who have triple-negative breast cancer tend to do the worst.

H&O Is treatment for brain metastases improving?

NL We have more options than we used to, but treatment has not improved enough. The treatments we use are radiation (either whole-brain radiation therapy or stereotactic radiosurgery [SRS]), surgery in some patients, and various systemic therapies.

H&O How do physicians decide between whole-brain radiation and SRS?

NL A big shift toward SRS has taken place over the past decade, which largely has been driven by the results of several randomized trials, specifically those reported by Soffiatti and colleagues, Aoyama and colleagues, and Chang and colleagues. In these trials, patients with up to 3 or 4 brain lesions underwent SRS either alone or in combination with whole-brain radiation. All of the studies showed that although the addition of whole-brain radiation delayed progression to the next central nervous system (CNS) event, overall survival did not improve, quality of life worsened, and neurocognitive problems developed. So for patients who present with a limited number of lesions that are small enough and in a location amenable to SRS, we use that approach in an attempt to minimize short- and long-term toxicity to the brain. Patients who present with multiple lesions, however, are still best served by whole-brain radiation.

H&O What are the best ways to reduce the risk for cognitive side effects from whole-brain radiotherapy?

NL The 2 main ways to reduce the risk for cognitive side effects from whole-brain radiotherapy are medication and alteration of the radiation treatment field. Memantine is the agent that has been most studied for this use. For example, the phase 3 RTOG (Radiation Therapy Oncology Group) 0614 trial by Brown and colleagues compared memantine vs placebo for prevention of cognitive dysfunction in patients receiving whole-brain radiation. Like most trials with radiation, this study enrolled mostly patients with non-small cell lung cancer; only a fraction of the patients had a primary diagnosis of breast cancer.

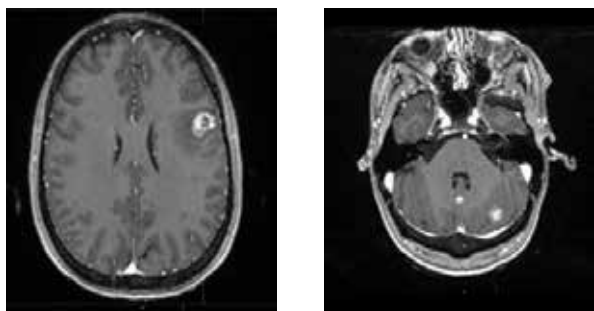


Figure. T1-weighted, post-gadolinium images demonstrating multiple brain metastases in patient with metastatic, HER2-positive breast cancer.

The researchers showed that at 24 weeks, the patients taking memantine had less cognitive decline than those taking placebo. The study was somewhat underpowered because the patients had poorer survival than expected; fewer patients were alive for assessment at the 24-week point than had been projected. Ultimately, however, whether the differences were statistically significant or simply trends, all of the endpoints measured favored memantine. As a result, many practitioners are routinely using memantine with whole-brain radiation.

The other approach to reducing cognitive side effects in whole-brain radiotherapy is the use of hippocampus-sparing techniques. In a single-arm trial conducted within the RTOG, in which a hippocampus-sparing approach to whole-brain radiotherapy was used, cognitive function was fairly stable at 4 and 6 months, the points at which cognitive function typically worsens with standard whole-brain therapy. Of course, despite the encouraging results, this was a nonrandomized study—we do not know whether the apparent difference was simply due to chance or patient selection. In an ongoing phase 3 study from NRG Oncology, NRG-CC001 (A Randomized Phase III Trial of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases; NCT02360215), all patients receive memantine and are randomly assigned to either standard or hippocampus-sparing whole-brain radiotherapy.

H&O Is there a limit to how many SRS treatments you recommend?

NL There is no hard and fast limit; it depends on the other options available to the patient. For example, I am much more likely to recommend systemic options rather than multiple rounds of SRS for a patient with HER2-positive breast cancer, for whom multiple systemic options are available. I am quicker to try salvage radiation in somebody who has triple-negative breast cancer, who

has fewer systemic options. The decision to attempt to use successive rounds of SRS really depends on the clinical situation and on whether we have systemic options with some reasonable chance of efficacy.

H&O When would you say that systemic therapy should be used?

NL Again, this is decided on a case-by-case basis. In HER2-positive breast cancer, for example, a number of regimens are available, but none of them is labeled specifically for the treatment of brain metastases in breast cancer. The regimens come with varying levels of data, however. For example, multiple single-arm trials (including one by my colleagues and me in *Clinical Cancer Research* in 2009 and one by Bachelot and colleagues in *Lancet Oncology* in 2013) have shown that capecitabine and lapatinib (Tykerb, Novartis) produce reasonable response rates in the brain—approximately in 20% to 25% in pretreated patients, and approximately 65% in patients who are not pretreated. So that combination certainly seems like a reasonable option.

In addition, relevant data exist regarding the antibody-drug conjugate ado-trastuzumab emtansine, or T-DM1 (Kadcyla, Genentech), which is approved for the treatment of HER2-positive metastatic breast cancer. Although we do not have prospective clinical trials, several case series from several different institutions have indicated that T-DM1 has activity in the brain, with response rates that are quite substantial.

We also recently completed a study that Dr Rachel Freedman presented at the 2017 American Society of Clinical Oncology annual meeting, in which neratinib (Nerlynx, Puma) plus capecitabine achieved a response rate of about 50% in the brain.

So, we have a number of different options. Capecitabine, lapatinib, T-DM1, and neratinib are commercially available, and additional agents are in development. The good response rates we have seen make these agents competitive with multiple rounds of SRS, and they offer a reasonable alternative to irradiation.

H&O What are some of the other systemic therapy options that are being studied right now?

NL We are very interested in bringing immunotherapy to the brain metastasis space in breast cancer. We know that immunotherapy has activity in brain metastases from lung cancer and melanoma, and we want to see if the same is true in breast cancer. The breast cancer trials to date have generally excluded patients with brain metastases. We have a trial looking at HER2-directed therapy plus atezolizumab (Tecentriq, Genentech) for HER2-positive

breast cancer, and we also have a study looking at SRS plus atezolizumab in patients with triple-negative breast cancer and brain metastasis (NCT03483012).

Dana-Farber, in collaboration with the Translational Breast Cancer Research Consortium (TBCRC), is also studying the use of neratinib plus capecitabine in HER2-positive breast cancer with brain metastases (NCT01494662), and later this year, a new arm will be added to this study in which neratinib will be combined with TDM-1. We also hope to open a number of additional studies over the next year based on our preclinical work; these studies may include work looking at brain-permeable phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitors, and at CDK4/6 inhibitor-based combinations.

H&O Do you keep patients on systemic therapy during radiotherapy?

NL If a patient is already taking pertuzumab (Perjeta, Genentech) or trastuzumab (Herceptin, Genentech), we usually continue it throughout the course of whole-brain radiotherapy. We have not seen any safety issues with continuing antibody-based therapy. We try to avoid giving cytotoxic chemotherapy during radiation because of concerns for increased toxicity. Unfortunately, multiple studies—many led by the RTOG—have found that a variety of agents are ineffective as radiosensitizers in whole-brain radiotherapy.

A different question is whether to switch systemic therapy after a diagnosis of brain metastases. For example, if a patient has received first-line therapy with a taxane plus trastuzumab and pertuzumab and 3 brain metastases develop during extended trastuzumab/pertuzumab maintenance treatment, I typically refer the patient for SRS and continue the treatment with trastuzumab/pertuzumab. However, if multiple brain metastases develop while the patient is on trastuzumab/pertuzumab, such that whole-brain radiotherapy would ordinarily be recommended, and if she or he does not have pronounced symptoms, I may recommend a switch to TDM-1 instead of whole-brain radiation, to see if radiation, which has long-term side effects, can be delayed. I also include clinical trial options in the mix and weigh with the patient the pros and cons of standard of care vs trial participation.

H&O How common is radiation necrosis, and how is it treated?

NL The incidence is not well quantified, for a couple of reasons. First, the ways in which radiation necrosis has been defined as a study endpoint have been inconsistent. Second, no gold standard test is available to distinguish absolutely between radiation necrosis and tumor progression. When

radiation necrosis occurs, it is typically in relation to focal radiation approaches—SRS, Gamma Knife radiosurgery, or the CyberKnife system. The treatment depends on the degree of necrosis. If the necrosis is radiographic only, we often just watch it to see whether it progresses. If the necrosis is symptomatic, meaning that the patient has edema and other related symptoms, we usually give corticosteroids. If the patient is not able to discontinue corticosteroids, we sometimes switch the patient to bevacizumab, which has been shown to provide symptom relief and to have corticosteroid-sparing effects.

H&O When is the resection of brain metastases indicated?

NL The resection of brain metastases is indicated in a number of situations. In the first situation, a patient presents with a solitary brain lesion and we need to obtain an accurate diagnosis. In the initial study by Patchell and colleagues comparing resection vs radiotherapy in patients with a single brain metastasis, 6 of 54 patients (11%) had to be excluded because the lesions were actually second primary tumors or inflammatory or infectious processes. If any sort of diagnostic uncertainty is encountered, we really need to nail down the diagnosis.

In the second situation, the patient is highly symptomatic. If a patient has only 3 brain lesions but one of them is very large and causing symptoms, an immediate response is needed. I would refer such a patient to surgery, which quickly relieves symptoms and allows the use of radiation afterward.

In yet another situation, when the patient has already received various treatments but a single lesion acts up at a later time, we might want to think about surgery to the isolated lesion that has progressed from a symptom management standpoint.

Finally, surgery might be used later in the disease course to distinguish between progression and symptomatic radiation necrosis.

H&O What are some of the challenges in designing clinical trials for patients who have breast cancer with brain metastases?

NL The first challenge is to make sure that the inclusion/exclusion criteria are sufficiently friendly—we do not want to exclude patients unnecessarily. Second, we want to make sure we are using the most consistent tools for assessing response. Many investigators are now starting to use the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria to report results. We are still determining whether the RANO-BM is the optimal measure, but at least it provides consistency across studies.

H&O Is there a way to prevent brain metastases?

NL We do not have a proven prevention strategy at this time. We had hoped that lapatinib/capecitabine, which has activity in the brain of patients with established brain metastases, might help prevent brain metastases. However, CEREBEL (Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in ErbB2 Positive Metastatic Breast Cancer), a randomized trial of capecitabine in combination with either trastuzumab or lapatinib in patients without evidence of brain metastases, found no difference between rates of CNS progression in the 2 groups—although this could have been a consequence of the small number of patients with CNS progression overall.

H&O What are the most important ongoing studies looking at the management of brain metastases?

NL One of the most important of the ongoing studies is the HER2CLIMB trial (Phase 2 Study of Tucatinib vs Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer; NCT02614794). HER2CLIMB is a phase 2 randomized trial of trastuzumab/capecitabine with or without the experimental oral HER2 inhibitor tucatinib in locally advanced or metastatic HER2-positive breast cancer. The trial was undertaken following the results of a phase 1 trial in which this triplet achieved a systemic response rate of about 60% and a CNS response rate of about 40%. The results of HER2CLIMB were presented by Dr Erika Hamilton at the 2016 San Antonio Breast Cancer Symposium.

HER2CLIMB is important because patients with active brain metastases are able to enroll. More trials need to be designed in this way, because brain metastases will eventually develop in about half of patients with advanced HER2-positive breast cancer. We have a

huge gap in our knowledge of how to take care of these patients in the clinic.

Disclosure

Dr Lin has received research funding from Array BioPharma, Cascadian Therapeutics, and Genentech.

Suggested Readings

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