Assessing Treatment Response in Metastatic Breast Cancer

Shlomit Strulov Shachar, MD, and Hyman B. Muss, MD

Abstract

Metastatic breast cancer remains incurable, and most patients receive endocrine therapy, chemotherapy, and/or biologic therapy over the course of their treatment. In spite of a plethora of new approved agents there have been no convincing major advances in the overall survival of patients with metastatic breast cancer, except for those with Human Epidermal Growth Factor Receptor-2 positive tumors. The goals of treatment in the metastatic setting are control or palliation of symptoms and maintaining the highest quality of life. In the last several years there have been major advances in imaging and new technologies, such as the measurement of circulating tumor cells, which have made assessment of treatment response more complicated. In this context, outside of a clinical trial, we will share our recommendations for addressing the challenge of assessing treatment response in patients with metastatic breast cancer.

Key words: metastatic breast cancer, treatment, response, imaging

Introduction

Breast cancer is the most common cancer and is the leading cause of cancer mortality in women worldwide, with more than 1.5 million new cases and over half a million deaths per year.[1] In the United States in 2016, 246,660 new cases of breast cancer are estimated, as well as 40,450 deaths due to metastatic disease.[2] Although there have been major advances in cancer treatment in the last decade, metastatic breast cancer (MBC) remains incurable; the current median survival after initial diagnosis of metastases is 2-3 years, with 5-year survival of about 25% and 10-year survival of about 10%.[3,4]

A few studies suggest major improvements in survival in MBC over the last several decades[5,6] while another study, after adjustment for other variables (such as disease-free interval), suggests no major changes.[4] Most newer agents convincingly improve progression-free survival but, with the exception of chemotherapy and anti-human epidermal growth factor receptor 2(HER-2) therapy in women with HER2-positive metastatic disease, they have had none or very modest effects on survival. In one classic study, Bloom and colleagues found that women who were diagnosed with breast cancer in the late 1800s and early 1900s but were never treated had a median survival of 2.7 years.[7] We believe that the modest survival benefit attributed to new systemic therapies is partially due to lead-time bias resulting from earlier diagnosis of metastatic disease with more sophisticated tests (tumor markers) or imaging such as computerized tomography (CT), radionuclide imaging, magnetic resonance imaging (MRI), and positron emission tomography (PET), that can detect metastases early when patients have minimal or no symptoms and a very low tumor burden.[5] This has resulted in many women being candidates for multiple systemic therapies.

In deciding on the optimal time for assessing patients with metastatic disease, it is important to be aware of response durations to available therapies. Bonotto et al studied the response durations to first-line and subsequent endocrine therapy or chemotherapy in 472 women with MBC and demonstrated that patients had the longest median progression-free survival to first-line treatment (7 to 9 months); survival decreased by 2 to 4 months for each subsequent line of treatment.[8] These data fit with those of numerous clinical trials, and suggest that the optimal response assessment strategy will vary greatly by type and line of therapy.

Treatment options are dependent on tumor phenotypes; while triple-negative tumors will respond only to chemotherapy, patients with HER2-positive tumors will gain a major benefit from adding targeted anti-HER2 agents to either endocrine therapy or chemotherapy.[9] Patients with hormone receptor (HR)-positive tumors can have a long progression-free survival with endocrine treatment alone or when combined with biological agents such as mTOR inhibitor or CDK4/6 inhibitors.[10,11] There are also a very small percentage of patients who have long-term responses to their metastatic lesions, but these represent a very small minority of those treated.[12]

Regardless of the treatment selected in the metastatic setting, therapy is palliative and the goals of treatment are to manage or prevent symptoms, improve quality of life and control disease progression with the least amount of physical, psychologic, or

TABLE 1. Recommendations for Assessment by Therapy Modality

Test	Endocrine Therapy	Chemotherapy	Comment
CBC, LFTs	2-3 months	Prior to each cycle	Dependent on agent
CT chest, abdomen and pelvis	2-6 months	Every 2–4 cycles[23]	No contrast needed for chest metastasis
Bone scan	4-6 months	4-6 months	Likely not helpful if metastasis not seen on CT of chest, abdomen, and pelvis and no symptoms in other bones not evaluated on CT
PET/CT	3-6 months*	3-6 months*	Use others above if less cost
MRI (Brain)	3 months*	3 months*	Most will have RT

Modified from Graham et al J Cancer 2014,[32] based on NCCN guidelines[23] and ESO-ESMO consensus guidelines for advanced breast cancer[22]
*authors recommendations
CBC indicates complete blood count; LFTs, liver function tests; CT, computerized tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; RT, radiation therapy.

financial toxicity. Treatment response by itself may not always be congruent with these goals, especially in patients with minimal symptoms who are having major toxicities from therapy. The optimal strategy for assessing the response of metastasis outside of clinical trials has not been rigorously defined; here we describe our approach to the assessment of treatment response in patients with MBC and highlight important key points in metastatic disease management.

Assessment

General Principles

Table 1 summarizes the general approach for assessing treatment response in a patient with MBC based on type of therapy and assessment modality. The cornerstone of assessment is the history and physical examination complimented by laboratory work (complete blood counts, liver function tests [LFT], and others). Imaging can include standard X-rays, radionuclide scans (bone), CT and/or PET/CT (lung, pleura, liver, and other), and MRI (best for assessment of central nervous system [CNS], brachial plexus, and spinal cord) with detailed recommendations below based on organ involvement. Of note, the type of imaging modality and its frequency of use should be based on clinical-pathological characteristics such as disease tempo, other comorbidities, and tumor burden. An excellent recent review of the different imaging modalities is available.[13]

For patients with cutaneous or palpable nodal metastases only, a physical examination alone should be sufficient for follow-up assessment with imaging done infrequently (such as every 3 to 6 months) in the absence of symptoms. Photographs of visible lesions should be added to the medical record when possible. For patients with additional metastatic sites along with skin or other palpable lesions that are easily monitored by physical examination, imaging can be done on a less-frequent basis, as the majority of patients who are responding or have stable disease in palpable lesions are likely to have similar responses in other sites. Even with extensive use of imaging modalities, the optimal use of these tools has yet to be defined.[13]

The most common imaging modalities used for assessment include:

X-ray: One of the oldest medical imaging methods, X-ray is fast, usually readily available, low cost, and generally does not require special preparation. This method can be especially helpful to define the fracture risk of bone metastases or monitor pulmonary lesions (when visible).

Technetium-99m radionuclide bone scan: This offers whole-body screening for bone metastases after intravenous administration of technetium-99 and has the same value in detecting bone metastasis as PET-CT.[14] The scan may not show purely lytic lesions.

Computerized Tomographic (CT) scan: This specialized X-ray technology is widely available and can be done with or without oral and intravenous contrast agents. Intravenous contrast agents should be used with caution or omitted in patients with renal dysfunction.

Magnetic Resonance Imaging (MRI): This more recent imaging technique is based on nuclear magnetic resonance and does

not involve radiation. It is the best tool for neuroimaging. The major limitations of this technique are its lack of availability in many locations, cost, and the length of time needed to complete imaging. In addition, the enclosed nature of MRI machines requires that patient movement be kept to a minimum, which may cause problems for patients with painful metastases or those with claustrophobia.

Positron Emission Tomography (PET): This is likely to be the best single test when done with concurrent CT imaging (PET/CT).[15] PET alone is a functional assessment of tumor metabolism while CT provides more accurate location and size data. Its high cost is a major detriment. In addition, the use of early metabolic response in patients receiving endocrine treatment can be difficult to interpret, mainly due to the early 'flare phenomenon' that can occur within the first 1 to 2 weeks after initiation of treatment.[16]

Assessment of Specific Disease Sites

Bone: Patients with bone metastasis, especially the approximately 20% of patients with MBC who have bone-only disease,[17] can be difficult to assess, especially within the first few months after starting therapy or after changing to a new treatment. Imaging of these patients at 3 months can be especially misleading, as some patients will have increased blastic lesions on CT that actually represent healing and not progression, as well as new lesions on radionuclide bone scan that represent healing of lesions that were not radionuclide avid on their initial scan.[18] CT can determine if bone lesions are lytic and/or sclerotic metastases, [19] while plain films should be used to assess weight -bearing bones for cortical damage (especially for the hips and femur).[19] After starting a new treatment, radionuclide scans should be avoided during the first 3 months in asymptomatic patients and in patients who may be having a tumor flare (see below).[18] For those with bone pain related to metastases, a convincing improvement in pain is probably the best evidence of a clinical response.

Lungs and Pleura: CT and PET/CT are the optimal imaging tools for initial assessment, but chest X-ray can be used for follow-up if lesions or effusions are easily seen.[20] CT without contrast can be used for the routine assessment of pulmonary nodules.

Liver: The optimal tools for assessment of the liver are physical examination (when the liver is easily palpable), liver function tests (LFTs), and contrast CT, PET/CT, and MRI can be used to help distinguish metastatic from non-metastatic lesions.[21] Ultrasound can be helpful in evaluating patients with increasing bilirubin for obstruction in the porta hepatitis.

Brain: Brain imaging only should be performed in symptomatic patients,[22,23] MRI with and without contrast is the imaging modality of choice for brain metastases. CT with and without contrast is also a good option, and should be considered when MRI is not available.[24] Scans should be done after completion of definitive therapy (surgery and or radiation) and followed periodically (every 3-6 months), thereafter in the absence of new signs and symptoms of CNS progression. MRI also is the optimal modality for evaluating patients for spinal cord compression and brachial plexus involvement.

Tumor flare

Tumor flare generally occurs within 1 to 4 months of treatment initiation and can occur with either endocrine therapy or chemotherapy.[18,25] Tumor flare can cause worsening of skin lesions if present, increasing bone pain, and hypercalcemia in those with bone metastases, and increases in LFTs and tumor markers. In one series, 29% of patients who ultimately responded to treatment had worsening of their bone scan 8 to 16 weeks from the initiation of therapy.[18] In those cases, PET/CT can be used, and the standardized uptake value (SUV) can be helpful.[26] Management should include reassurance, careful observation, and in some patients, glucocorticoids.

Tumor Markers (CA 27.29, CA 15.3, CEA) and Circulating Tumor Cells

We recommend assessing a tumor marker at the initiation of therapy to serve as a baseline. Only 1 marker is needed, and we favor CA 27.29 because it has the greatest sensitivity.[27] Of note, in approximately 25% of patients with metastases, tumor markers are normal. We do not recommend them for routine follow-up if other easily evaluable or measureable disease is present. If tumor markers are used for follow up, a rise in markers alone (at least 2 separate values increasing by more than 20% to 30% from the previous value) should not be used to change treatment; progression on examination or imaging should be noted as well. One of the major disadvantages of using tumor markers to monitor treatment is the fear and distress noted by the patient while awaiting results, or when there are small increases of questionable significance.[28]

Circulating tumor cells (CTC) can be detected in peripheral blood and are defined as the number of tumor cells per mL in a whole blood sample (eg, ≥5 CTC/7.5mL of whole blood). In a large study (n = 595) of patients with MBC receiving first-line chemotherapy, the number of CTCs was a significant prognostic factor, while early switching to different treatment regimen as compared to remaining on the initial treatment did not improve overall survival.[29] Of note, almost half of the patients screened for this study did not have CTCs. Although the presence of CTCs are highly correlated with imaging results,[30] we do not recommend their routine use for assessing response.

Conclusions

MBC remains a clinical challenge, and the average median survival still remains about 3 years from initial discovery of cancer spread. Although costly and detailed assessment using the well-established RECIST criteria[31] is appropriate for most clinical trials, response assessment outside the trial setting should mini-

mize testing unless necessary for assessing continuing or worsening signs and symptoms. For metastases that can be monitored through physical examination (such as skin lesions or palpable breast or nodal masses), physical examination can suffice with imaging used at longer intervals. For liver metastasis, following liver enzymes in patients with initial elevations is most helpful with imaging reserved for the confirming progression. For pulmonary or pleural metastases, chest X-rays when positive can be used to adequately monitor patients. Although there are no compelling guidelines or standards of care for assessing response outside of a clinical trial, periodic imaging with CT, PET/CT, or radionuclide scans is prudent but can be done at longer intervals (ie, 6 months) in patients where physical examination or laboratory tests can be used for monitoring. Minimizing the use of imaging and laboratory work, unless needed to confirm disease progression, determine the cause of new symptoms, or as baseline for new treatment, is probably the most cost effective strategy for monitoring the majority of patients with metastatic breast cancer.

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Affiliations: Shlomit Strulov Shachar, MD, and Hyman B. Muss, MD, are from Department of Medicine, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC. Shlomit Strulov Shachar, MD, is also from Division of Oncology, Rambam Health Care Campus, Haifa, Israel.

Address correspondence to: Hyman B. Muss, MD, 170 Manning Drive, CB 7305 Chapel Hill, NC 27599. E-mail: muss@med.unc.edu.

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