Treatment of Metastatic Breast Cancer

Presented by William J. Gradishar, MD

Abstract
Many newer agents in combination are being studied in the front-line treatment of women with HER2-positive metastatic breast cancer (MBC), but the story in the endocrine arena is more about the wise use of new strategies to overcome endocrine resistance, because no new antihormonal agents have been approved in the past decade. During his presentation at the NCCN 19th Annual Conference, Dr. William Gradishar explored what’s new in the treatment of MBC, focusing primarily on enhancing the effect of endocrine therapy to overcome resistance with newer targeted agents such as everolimus, reevaluating the role of rebiopsy on disease progression and measuring circulating tumor cells as a surrogate of response to treatment, and reviewing the effective treatment regimens for HER2-positive disease. (J Natl Compr Canc Netw 2014;12:759–761)

“T”here are lots of endocrine agents for treating hormone-positive metastatic breast cancer. For relapsed/refractory disease, the data do not support that one sequence is better than the other,” revealed William J. Gradishar, MD, Betsy Bramsen Professor of Breast Oncology, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and Chair of the NCCN Breast Cancer Panel. Therapeutic decisions for metastatic breast cancer (MBC) center on considerations such as the pace of the disease, the patient’s overall medical condition, and comorbidities. Dr. Gradishar reviewed the current clinical data on endocrine therapy and strategies to overcome endocrine resistance, and discussed new agents used in treatment of metastatic HER2-positive disease.

Newer Strategies for Overcoming Endocrine Resistance

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommend treating recurrent invasive breast cancer showing visceral symptoms with endocrine therapy until disease progression, unless the toxicity is unacceptable. On disease progression, if symptomatic visceral disease is detected, then chemotherapy is an option. However, if a clinical benefit is seen with initial endocrine therapy and symptomatic visceral disease is not present, a trial of a new endocrine therapy is indicated.

For subsequent endocrine therapy, “there is no algorithm or sequence that is always optimal,” acknowledged Dr. Gradishar. He then noted that the effect of endocrine therapy may be enhanced by combining it with newer agents.

Dr. Gradishar briefly reviewed 2 studies that assessed the role of combination endocrine therapy, with conflicting results reported.1,2 The FACT phase III study compared combination anastrozole and fulvestrant with anastrozole alone in the first-line treatment of postmenopausal women with receptor-positive breast cancer.1 They found that the combination offered no clinical efficacy advantage over monotherapy. However, the SWOG clinical trial showed that the combination of anastrozole and fulvestrant was superior to anastrozole alone in the treatment of women with hormone receptor–positive MBC.2 The statistically significant improvement in outcomes
was limited to the group of patients who had not been exposed to adjuvant tamoxifen. Dr. Gradishar questioned whether this outcome was clinically relevant. He stated that even though the SWOG trial may support administering combination therapy in first-line treatment, using combination therapy upfront would reduce subsequent therapy options. Thus, the role of combination endocrine therapy as first-line treatment remains to be clearly defined.

Several trials have tested combining hormone therapy in women with advanced breast cancer after disease progression on nonsteroidal aromatase inhibitors (AIs). For instance, the phase III SoFEA trial revealed that combining fulvestrant with exemestane was no better than either fulvestrant alone or exemestane alone after the loss of response to nonsteroidal AIs in postmenopausal women with hormone receptor–positive MBC.

Clinical strategies for overcoming resistance to endocrine therapy that have gained interest recently involve using the mTOR inhibitor everolimus in combination with exemestane, the CDK inhibitor PD 0332991 in combination with letrozole, and the Src inhibitor dasatinib in combination with letrozole. According to Dr. Gradishar, the TAMRAD phase II trial that combined tamoxifen and everolimus “was the first study to hint that by targeting mTOR you could overcome endocrine resistance.” In a much larger and definitive study, Baselga et al found that the response rate and clinical benefit favored the combination of everolimus and exemestane versus exemestane and placebo in postmenopausal women who had received prior therapy with a nonsteroidal AI. Thus, everolimus in combination with exemestane is currently included in the NCCN Guidelines as a subsequent therapy option for women who have received previous therapy with a nonsteroidal AI.

Finn et al conducted a phase II study of letrozole alone or in combination with the CDK inhibitor, PD 0332991, as the first-line treatment of women with estrogen receptor–positive, HER2-negative MBC. Dr. Gradishar called the improvement in progression-free survival with the doublet “remarkable” (26.0 vs 7.5 months), and mentioned that a phase III trial to confirm these promising initial results is underway.

The use of the Src inhibitor dasatinib in combination with letrozole was assessed in a phase II study of postmenopausal women with hormone receptor–positive, HER2-negative MBC receiving first-line AI therapy. The clinical benefit rate was about the same with the doublet compared with letrozole alone, but the median progression-free survival improved from 9.9 to 20.1 months with the addition of dasatinib.

“There was a doubling of progression-free survival with the combination of the Src inhibitor and the endocrine agent, which is similar to what we saw with the mTOR and CDK inhibitors,” noted Dr. Gradishar. Dr. Gradishar pointed out that a very interesting finding from this trial was that blocking Src leads to a significant improvement in bone density.

### Update on the Role of Rebiopsy and Circulating Tumor Cell Levels

Dr. Gradishar provided an update on the impact of rebiopsy in patients with disease recurrence and measuring circulating tumor cell (CTC) levels on subsequent treatment decisions in women with advanced breast cancer. In his opinion, rebiopsy has a current role but measuring CTC levels does not.

The discordance reported in the hormone and HER2 marker status (between 0% and 38%) between primary and recurrent disease is the rationale behind rebiopsy, Dr. Gradishar explained. He stated that it is prudent to rebiopsy, particularly if there is a long interval between original diagnosis and disease recurrence and limited sites of recurrence that are easily accessible to biopsy to ensure that the marker status is consistent with the original diagnosis. The biopsy results may lead to change in treatment strategies and ensure that patients are not inadvertently denied effective therapies.

The issue with CTCs hinges on whether the information obtained from their measurement can be used to alter therapeutic decisions and impact overall outcomes. “We have known about circulating tumor cells for years now,” admitted Dr. Gradishar. “If the number of circulating tumor cells is going up, it is probably not a good thing, and if it is going down, it may be a good prognostic sign.”

A recent phase III SWOG trial tested the strategy of changing versus maintaining therapy for patients with MBC who had elevated CTC levels at their first follow-up assessment. The investigators found no apparent difference in overall survival whether therapy was maintained or switched, said Dr. Gradishar. “So at the present time, using circulating tumor cells as a surrogate or measure of effectiveness of therapy is not supported by the data,” he concluded.
Novel Anti-HER2 Therapies

Patients with HER2-positive breast cancer benefit from HER2-targeted therapy. The addition of trastuzumab to chemotherapy has significantly improved outcomes and overall survival for these patients. Many newer drugs are being evaluated in combination with trastuzumab for the treatment of HER2-positive disease.

The combination of pertuzumab, trastuzumab, and docetaxel is a new category 1 preferred option for first-line therapy of patients with HER2-positive breast cancer listed in the current NCCN Guidelines for Breast Cancer. This recommendation is based on clinical trial data from more than 800 patients with HER2-positive MBC. Compared with trastuzumab plus docetaxel, this trial showed that triple-drug regimen significantly prolonged progression-free and overall survivals. Paclitaxel could be used instead of docetaxel in this triplet, and this is noted in the NCCN Guidelines for Breast Cancer. Trastuzumab in combination with eribulin mesylate has shown encouraging results in patients with HER2-positive MBC in the first-line setting. In a phase II single-arm study, the combination of trastuzumab and eribulin mesylate seemed to offer a benefit in terms of overall response rate and progression-free survival.

New HER2 targeting drugs have shown benefit in recurrent disease. In the EMILIA study, T-DM1 was reported to be more beneficial than capecitabine and lapatinib in nearly 1000 patients with HER2-positive advanced breast cancer previously treated with a taxane-trastuzumab regimen. The progression-free survival favored T-DM1 (9.6 vs 6.4 months), said Dr. Gradishar, and appears to also have an overall survival benefit. Similarly, the TH3RESA trial compared TDM-1 with the treatment of physicians’ choice. Patients enrolled in this trial received at least 2 previous lines of therapy for metastatic disease in addition to trastuzumab and lapatinib and were experiencing disease progression on these agents. In the preliminary analysis, T-DM1 has demonstrated improved efficacy with significant improvement in progression-free survival, reaffirming the results from the EMILIA study and the benefits of T-DM1. Other studies are testing T-DM1 in the first-line setting, including the ongoing phase III MARIANNE trial, which is comparing 3 treatment arms: the combination of a taxane and trastuzumab, T-DM1 alone, and T-DM1 plus pertuzumab.

References