Optimizing Treatment of HER2-Positive Breast Cancer

Presented by William J. Gradishar, MD

Abstract

The treatment of HER2-positive breast cancer has benefited from a number of targeted agents. Although adjuvant trastuzumab has dramatically reduced progression—making metastatic disease far less common today—newer treatment advances are also impacting this disease. Dual targeting with pertuzumab and trastuzumab can extend the survival of metastatic disease by more 16 months, but despite such success, resistance to HER2 targeting remains a challenge. Drugs in the pipeline, such as neratinib, may help meet this therapeutic demand. In addition to anti-HER2 agents, chemotherapy is beneficial to patients with tumors 1 cm or larger, but the optimal treatment of smaller tumors is still a work in progress.
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Since ErbB2 (HER2) was first recognized in the 1980s as an oncogenic driver of breast cancer, treatment of patients with HER2 overexpression has advanced at a steady pace. Recognition has also grown that HER2-positive disease is heterogeneous, and that management must parallel its complexity, according to William J. Gradishar, MD, Director of the Maggie Daley Center for Women's Cancer Care at Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and Chair of the NCCN Guidelines Panel for Breast Cancer, who described these tumors at the NCCN 20th Annual Conference.

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With a greater understanding of the initial management of patients with a HER2-positive tumor, the NCCN Guidelines Panel for Breast Cancer have refined the guideline recommendations to address "ambiguity" in HER2 expression. "Reflex testing" is done based on HER2/CEP17 ratio, HER2 copy number, and in situ hybridization (ISH) status.

"Not all HER2-positive disease is HER2-enriched, and plenty of other subtypes can be HER2-positive," Dr. Gradishar explained. "We think broadly about our treatments, but the reality is that intrinsic subtypes may be a little promiscuous."

The efficacy of adjuvant trastuzumab has translated into a much lower incidence of metastatic disease and less need for additional anti-HER2 treatment. These early findings "gave proof of principle that targeted treatment really can change the clinical course of cancer," he said.

But some patients still experience recurrence and some present with de novo metastatic breast cancer. For the latter, a dozen or so recommended treatment options exist, based largely on understanding the value of continuously leveraging the HER2 pathway. One key discovery in this area was the relative efficacy of dual targeting of the HER2 pathway. In an important study by Blackwell et al,[1] trastuzumab plus lapatinib reduced progression by 27% (P=.008) over single-agent trastuzumab.

Further, understanding that HER2:HER3 dimers may help tumors escape the effect of trastuzumab led to the development of pertuzumab, which inhibits ligand-dependent HER2 dimerization and signaling. The landmark CLEOPATRA trial demonstrated the dramatic value of combining these 2 drugs in combination with chemotherapy: overall survival was increased by 15.7 months versus trastuzumab alone (P=.0002).[2]

"Relatively few treatment regimens can claim to improve overall survival in excess of 1 year," he said. "CLEOPATRA firmly placed trastuzumab/pertuzumab as the most effective first-line treatment for metastatic HER2-positive breast cancer."

Importantly, the combination was well tolerated, with no significant increase in risk of cardiac events. Pertuzumab/trastuzumab was given with docetaxel in CLEOPATRA, but NCCN Guidelines allow other taxanes to be substituted. Several ongoing trials are now evaluating whether dual blockade given for 1 full year in the adjuvant setting might further improve outcomes, and whether subsets of patients will receive greater relative benefit from the combination.

Although dual HER2 blockade prolonged survival in the metastatic setting and increased rates of pathologic complete response (pCR) in the neoadjuvant setting, surprisingly, dual blockade with lapatinib plus trastuzumab (and chemotherapy) did not improve outcomes in the adjuvant setting. Failure to improve outcomes in the ALTTO trial[3] indicated that pCR does not strictly correlate with long-term outcomes. In fact, the meaning of pCR appears to depend on tumor subtype, defined by estrogen receptor and HER2 status, according to a meta-analysis by Cortazar et al[4] and the results of trials such as NeoSphere.[5] Even within a clinical subset, pCR is affected by treatment, tumor genetics, and the microenvironment (eg, tumor infiltrating lymphocytes), a recent study suggested,[6] according to Dr. Gradishar.

"In short, achievement of pCR *may* improve breast cancer outcomes, but it may be true only for extraordinary drugs," he commented.

New Drug Class

Patients with HER2-positive disease are also benefiting from the development of a unique fusion molecule, the antibody-drug conjugate T-DM1. For previously treated patients in the EMILIA trial, T-DM1 reduced mortality by 22% ($P<.001$) over capecitabine/lapatinib, without serious toxicity concerns.[7] The TH3RESA study reaffirmed these findings with a 47% reduction in progression ($P<.0001$) versus physician's choice of treatment.[8]

Unfortunately, when T-DM1 was "moved up" to the first line, no significant improvements in end points were shown in the phase III MARIANNE trial, although details are not yet available, he added.

Overcoming Resistance

The current challenge in this disease is modulating or overcoming resistance to HER2 therapies in metastatic disease by somehow "perturbing the pathway," he said. The phase III BOLERO-3 trial randomized patients with trastuzumab-resistance to vinorelbine and trastuzumab, with and without the mTOR inhibitor everolimus. The study showed a statistically significant ($P=.0067$) but clinically modest 1.3-month progression-free survival benefit.[9]

In the first-line setting of the BOLERO-1/TRIO 019 trial, trastuzumab/paclitaxel/everolimus did not improve progression-free survival overall. However, in the hormone receptor–negative subgroup, progression was reduced by 34% ($P=.0049$) in the everolimus arm.[10]

"You have to argue whether this is moving the ball down the field," Dr. Gradishar commented. The NCCN Guidelines do not currently recommend trastuzumab/paclitaxel/everolimus for trastuzumab-exposed patients.

The hope is that neratinib, a potent, orally available, irreversible pan-ErbB kinase inhibitor might be active for patients who experience disease progression on anti-HER2 agents. The NALA trial, a global phase III registration study that randomized heavily pretreated patients to neratinib/capecitabine or lapatinib/capecitabine, will be informative, in addition to further data from the I-SPY 2 neoadjuvant trial, which evaluated neratinib plus trastuzumab or placebo in a variety of HER2-positive subsets.[11] The addition of neratinib increased pCRs, pointing to significant antitumor activity. "Whether we can use this agent broadly remains to be seen," Dr. Gradishar commented.

Management of Small Tumors?

Patients with HER2-positive T1a or T1b, node-negative disease tend to have good long-term outcomes, with distant relapse-free survival rates of 94% to 100% after chemotherapy plus trastuzumab. However, recurrences can be observed. The value of HER2-targeted treatment in these small tumors has been hard to determine.

A meta-analysis of randomized adjuvant trastuzumab trials focusing on patients with tumors 2 cm or smaller and 1 or fewer positive nodes documented substantial benefit in terms of both disease-free and

overall survival for trasatuzumab therapy, but almost all patients had T1c disease and positive axillary nodes.[12] This is a very select group of patients. "We cannot cull out many patients with tumors less than 1 cm," he said.

Dr. Gradishar further noted that chemotherapy use has been steadily increasing among patients with HER2-positive T1a or T1b disease. A recent study of 400 node-negative patients with tumors 3 cm or smaller showed a 3-year disease-free survival rate of 98.7% with trastuzumab plus paclitaxel.[13]

"It's hard to improve on this outcome, with this nonanthracycline regimen," which may be appropriate for patients with cardiac concerns, he said.

The 2015 NCCN Guidelines recommend trastuzumab plus chemotherapy for patients with HER2-positive, hormone receptor–negative disease and with tumors 1 cm or greater. The NCCN Guidelines also list several "considerations" for smaller tumors. For many clinicians, the threshold for using trastuzumab is T1cN0, but the true threshold is unknown. The ongoing ATEMPT trial should help to further define the value of chemotherapy in these patients.

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