Oncology

New Research on the Treatment of Small HER2-Positive Breast Cancers

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H&O What are some of the challenges of managing small human epidermal growth factor receptor 2 (HER2)-positive breast cancers?

IK The optimal approach to managing patients with small HER2-positive breast cancers has long been a clinical dilemma for physicians.

We know that trastuzumab (Herceptin, Genentech) is very effective as adjuvant therapy in HER2-positive breast cancer; a number of large clinical trials clearly show that adjuvant trastuzumab cuts the risk of recurrence by approximately 50%. As a result, trastuzumab-based chemotherapy is the standard of care for patients with higher-risk HER2-positive early-stage disease.

The limitation of this research has been that virtually all the patients in these trials had fairly high-risk disease; either their cancers were large or they had significant lymph node involvement. Most of the trials excluded lymph node-negative cancers, and the trials that did include a small number of lymph node-negative cancers typically included only larger cancers. Few of the patients in the trials had small cancers. As a result, we do not have good data to say whether trastuzumab is appropriate therapy for small cancers.

We do have a handful of retrospective studies that have looked at the recurrence rate of HER2-positive cancers that are smaller than 2 cm. As it turns out, the recurrence rate of these cancers is higher than one might expect when adjuvant therapy is not used—most of the studies have shown a recurrence rate between 20% and 30%. Although some studies have found a somewhat lower recurrence rate, the weight of the evidence would suggest that a small HER2-positive cancer, particularly one that is greater than 1 cm in size, still has a significant risk of recurrence without systemic therapy. I feel that most patients with this type of tumor will benefit from adjuvant therapy even though this has not yet become the standard of care.

In the absence of clear guidelines, oncologists have been using a fairly wide variety of approaches to treat small breast cancers. Some oncologists use the same multiple-agent chemotherapy regimens that we use for high-risk patients, while others use trastuzumab alone, chemotherapy alone, or endocrine therapy alone, but the fact that there is no standard makes the decision difficult.

H&O Could you talk about your recent trial in women with small HER2-positive breast cancers?

IK We were struggling at Dana-Farber with the question of how to treat women with small HER2-positive breast cancers, and we felt that the way to address that was to undertake a prospective study of these patients. Our hypothesis was that because these are lower-risk cancers, we might be able to take advantage of the benefit of trastuzumab and use a less-intensive chemotherapy regimen than is used for higher-risk patients.
The trial, which was led by my colleagues Drs Sara Tolaney and Eric Winer, included 406 patients with breast cancers that were HER2-positive, node-negative, and less than 3 cm. The patients in this single-arm trial were treated with 12 weeks of weekly paclitaxel with concurrent trastuzumab followed by additional trastuzumab monotherapy to complete 1 year.

As we recently reported at the 2013 San Antonio Breast Cancer Symposium, the disease-free survival rate was 98.7% at a median of 3.6 years of follow-up. Of the 10 cases of breast cancer that occurred during follow-up, just 2 represented distant recurrences and the rest were either new primary tumors or locoregional recurrences.

Based on the results of this study, I believe that paclitaxel plus trastuzumab is a reasonable standard of care for patients with negative lymph nodes whose tumors are less than 3 cm. More than half of the patients on the study had tumors that were between 1 and 3 cm; about 9% of the patients had tumors between 2 and 3 cm. The remaining tumors were split between T1a and T1b. Overall, this variation reflects the type of patients we currently see in clinical practice.

**H&O Are there certain patients who can be treated with trastuzumab alone?**

**IK** We considered a trastuzumab-alone arm in this trial. However, when you look at the data in the metastatic setting, it is clear that the synergy between trastuzumab and chemotherapy is substantial. Based on this synergy, we felt it made more sense to look at the combination rather than trastuzumab alone. Are there patients you could treat with trastuzumab alone? Possibly, but I do not feel comfortable using that as a regimen because no long-term data exist saying that this is an effective regimen for patients in the adjuvant setting.

**H&O What other recent studies apply to the treatment of patients with HER2-positive breast cancers?**

**IK** Several studies have addressed the question of which cancers may be especially sensitive to HER2-directed therapies because of their molecular characteristics.

In 1 arm of the NeoSphere trial by Gianni and colleagues, which was published in 2012 in *Lancet Oncology*, 107 patients were treated with HER2-directed therapy—a combination of trastuzumab and pertuzumab (Perjeta, Genentech)—and no chemotherapy. Of these, 17% had a complete pathologic response to this biological therapy alone.

In a Translational Breast Cancer Research Consortium trial, which was led by Rimawi and published in 2013 in the *Journal of Clinical Oncology*, 66 women with stage 2 to 3 HER2-positive breast cancer received trastuzumab and lapatinib (Tykerb, GlaxoSmithKline) once per day for 12 weeks. A total of 27% of the patients experienced a pathologic complete response to treatment.

These trials support the idea that certain patients with HER2-positive tumors do not need chemotherapy, but we still do not know which patients these are. If we could identify up-front the patients whose cancer is extremely sensitive to HER2-directed therapy, we could consider using these agents in these patients without chemotherapy.

We did gain some interesting information from a study by Gebhart and colleagues that was published in the *Journal of Nuclear Medicine* in 2013. This study looked at patients in the Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial, which compared neoadjuvant trastuzumab with lapatinib and with a combination of trastuzumab and lapatinib, first with the biological therapies alone, then with the addition of chemotherapy. The researchers in this study analyzed the results of 18F-fluorodeoxyglucose–positron emission tomography/computed tomography, and found that early response as measured by this test was predictive to some extent of eventual pathologic complete response. Although patients in this study did receive subsequent chemotherapy, which limits the applicability of this research, the opportunity to use some type of early analysis as a way to identify those patients who might not need the addition of chemotherapy is a very interesting idea that is in the process of being tested. As our HER2-directed therapies get better and better, we hope to be able to get by with less and less chemotherapy and eventually identify those patients who do not need chemotherapy at all.

**H&O What are the mechanisms behind resistance to HER2 blockade?**

**IK** We do not have a great answer to that question, although a number of mechanisms have been proposed. One possibility is the presence of alterations in the HER2 protein that make it unable to bind to trastuzumab; the data on the validity of this idea have been mixed so far. Another possible mechanism is the presence of alterations in the signaling pathways downstream of HER2 that may cause the pathways to become constitutively active, rendering blockade of HER2 less effective. Mutations in the phosphoinositide 3-kinase (PI3K) gene represent a potential example of this type of mechanism. PI3K is a very important signaling protein downstream of HER2 that is mutated in a substantial proportion of HER2-positive cancers—probably somewhere around 20% to 25%. Several recent studies have shown that HER2-
positive cancers that have a \( P13K \) mutation appear to do worse than those who do not have the mutation when treated with HER2-directed therapy. The CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer) trial, which looked at the combination of trastuzumab and pertuzumab, showed worse outcome for patients with \( P13K \) mutated cancer, regardless of whether they received pertuzumab. The CLEOPATRA study was published in *Lancet Oncology* in 2013.

Patients with mutations in \( P13K \) also have worse outcomes when treated with capecitabine (Xeloda, Genentech) and lapatinib, according to the EMILIA (An Open-label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial. More recently, José Baselga presented data from the Neo-ALTTO trial at the 2013 European Society for Medical Oncology meeting showing that cancers with a mutation in \( P13K \) had a lower response rate to treatment with trastuzumab, lapatinib, or both drugs in combination compared with those tumors with wild-type \( P13K \). Together, these data support the hypothesis that 1 mechanism of resistance to HER2-directed therapy is dysregulation of the PI3K pathway.

**H&O** What approach do you recommend for small HER2-positive breast cancers that are resistant to anti-HER2 agents?

**IK** There is no way to monitor response to treatment in patients whose cancer has already been resected. As a result, we are not able to ascertain resistance in real time in those patients treated in the adjuvant setting. In the neoadjuvant setting, we do not have convincing data that switching therapies based on initial clinical response is beneficial. Therefore, I recommend that oncologists choose a standard regimen and continue it regardless of the patient's response unless the patient has progressive disease while on that therapy, which is rare.

**H&O** How do you decide whether patients should receive adjuvant or neoadjuvant therapy?

**IK** Until recently, the use of preoperative therapy was generally reserved for those patients in whom significant downstaging of the tumor was needed. What changed recently is that the US Food and Drug Administration approved the use of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting, and not in the adjuvant setting. As a result, the only way to use pertuzumab outside of a trial is to use it preop-

**IK** I do omit chemotherapy in certain patients. For example, the benefits of chemotherapy are likely to be small in patients who have competing risks of mortality because of other health problems or their age. The benefits of chemotherapy also may be small in patients whose cancer is very low risk, such as a 5-mm cancer that is ER-negative and HER2-positive.

**H&O** What new types of HER2-targeted agents are being developed, and which of these might play a role in treating small breast cancers?

**IK** Two HER2-targeted therapies that are relatively far along in development are being evaluated in the early-stage setting. One is pertuzumab, which has been approved for first-line metastatic disease and, as we discussed earlier, has now been approved for the neoadjuvant setting and is currently being evaluated in the adjuvant setting. A study called APHINITY (A Study of Pertuzumab in Addition to Chemotherapy and Herceptin [Trastuzumab] as Adjuvant Therapy in Patients With HER2-Positive Primary Breast Cancer) on the use of pertuzumab in the adjuvant setting has already completed enrollment. We potentially could see results from this study in 2016.

Another agent that is being developed is ado-trastuzumab emtansine, or T-DM1 (Kadcyla, Genentech), which has also been approved in the metastatic setting and is in the process of being tested in large adjuvant trials as well as in neoadjuvant trials. The results of these trials have the potential to change practice.

Both APHINITY and most of the ado-trastuzumab emtansine trials are focused on higher-risk patients; generally those with positive lymph nodes or large cancers. Our research group at Dana-Farber has been building on our recent work by opening another trial for patients with small, node-negative, HER2-positive cancers that is comparing ado-trastuzumab emtansine with paclitaxel and trastuzumab. As with the previous trial, the goal is to further reduce the toxicity of therapy by making use of improved HER2-directed therapies that allow us to potentially dial back the amount of chemotherapy we give to patients.
Suggested Readings


