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Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer

Resources

PER Pulse™ Recap
Three PER Pulse™ Recaps presenting key breast cancer treatment topics.

PER Pulse™ Recap

Medical Writer: Jennifer Klem, PhD

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PER Pulse™ Recap
Incorporation of Pertuzumab Into Management of HER2-Positive Metastatic Breast Cancer

The online CME activity, *Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer*, featured breast cancer experts Drs. Joyce O'Shaughnessy and Sandra Swain commenting on a case of a woman diagnosed with early-stage breast cancer in 1998 that metastasized 3 years after adjuvant chemotherapy and tamoxifen. They discussed the ongoing management of that patient, as well as current therapy options if that patient were being treated today. This first of 3 PER Pulse™ Recaps focused on *Oncology Consultations*™examines the incorporation of pertuzumab into the management of HER2-positive metastatic breast cancer (MBC).

The patient who was presented in the case study progressed to MBC after being treated in the adjuvant setting with chemotherapy and tamoxifen for her early-stage hormone receptor-positive disease (HER2 status unknown at the time). After biopsy revealed HER2-positive and hormone receptor-negative MBC, the patient was treated in the first line with trastuzumab plus vinorelbine; however, Dr. O'Shaughnessy pointed out that trastuzumab plus chemotherapy is no longer the standard of care for first-line HER2-positive MBC treatment, and the CLEOPATRA trial is the reason for this.

The phase III CLEOPATRA trial was designed to evaluate dual HER2 inhibition through the addition of pertuzumab, a HER2-directed antibody, to trastuzumab and docetaxel for HER2-positive MBC. Results showed that the pertuzumab-containing regimen had a 6.1-month advantage in median progression-free survival (PFS; $P < .0001$), as well as an overall survival (OS) advantage compared with the placebo-containing regimen (median not reached in the pertuzumab arm; $P = .0008$). The toxicity profiles of the two treatment groups were similar, and Dr. Swain pointed out that cardiac toxicity was not increased in the pertuzumab arm, providing reassurance of the cardiac tolerability of dual HER2 inhibition.

As a result of this trial, pertuzumab plus trastuzumab plus docetaxel was approved by the US Food and Drug Administration, and pertuzumab plus trastuzumab plus taxane has been recommended by the National Comprehensive Cancer Network as a preferred regimen for the first-line treatment of HER2-positive MBC. While both Drs. Swain and O'Shaughnessy agreed that dual HER2 blockade is the new standard of care for first-line HER2-positive MBC, both also clarified that they would combine pertuzumab and trastuzumab with weekly paclitaxel, based on personal preference for paclitaxel over docetaxel, and based on a phase II trial of the paclitaxel-containing regimen, which showed a 76% PFS rate at 6 months and a favorable safety profile.

In addition to being combined with trastuzumab, pertuzumab is also being studied in combination with ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and the cytotoxic agent DM1. The three-arm MARIANNE trial compares ado-trastuzumab emtansine in combination with pertuzumab or placebo versus the control regimen of trastuzumab combined with a taxane in patients with newly diagnosed MBC. This trial is fully accrued but is not expected to be completed until 2016.

Drs. Swain and O'Shaughnessy also discussed the use of pertuzumab in later lines of therapy, a setting that is currently off-label. Dr. O'Shaughnessy explained that limited data in the relapsed/refractory setting show clinical benefit of dual HER2 inhibition, leading her to suggest that it is a reasonable approach to the management of relapsed/refractory HER2-positive MBC. However, she cautioned that randomized data might be necessary if a dual HER2 inhibition regimen is to become a standard of care. Dr. Swain countered that randomized data may not even be necessary, suggesting that well-designed phase II trials in later lines of therapy could provide sufficient evidence.

For additional commentary about these topics and others, visit www.gotoper.com to access archived video of Dr. Swain and Dr. O'Shaughnessy from *Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer*.

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PER Pulse™ Recap
Trastuzumab for Long-Term Non-Progressors

The online CME activity, *Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer*, featured breast cancer experts Drs. Joyce O'Shaughnessy and Sandra Swain commenting on a case of a woman diagnosed with early-stage breast cancer in 1998 that metastasized 3 years after adjuvant chemotherapy and tamoxifen. They discussed ongoing management of that patient, as well as current therapy options if that patient were being treated today. This second of 3 PER Pulse™ Recaps from *Oncology Consultations*™ focuses on the subset of patients with metastatic breast cancer (MBC) who derive long-term clinical benefit from trastuzumab.

For patients with HER2-positive MBC, trastuzumab therapy is typically continued, alone or in combination with chemotherapy, until progression or unacceptable toxicity. In the observational registHER study of over 1000 patients with newly diagnosed HER2-positive MBC, median progression-free survival (PFS) with trastuzumab-based therapy in the first-line setting was 11.0 months. However, a subset of these patients has been identified that receives long-term clinical benefit from trastuzumab.

Several case reports and retrospective studies have described patients with MBC who have maintained remissions on trastuzumab for durations ranging from 3 years to nearly 12 years. However, as with the patient featured in this *Oncology Consultations*™, there are multiple examples of recurrence after discontinuation of trastuzumab.

Dr. O'Shaughnessy discussed how these data suggest to her that trastuzumab discontinuation for these patients is dangerous due to the risk of recurrence, but she acknowledged that other clinicians have interpreted these data differently. She shared an example of a clinician who realized that following discontinuation after receiving long-term

intermittent therapy.

As Dr. Swain mentioned, little is known about the clinicopathologic features associated with patients who derive long-term clinical benefit from trastuzumab therapy, and efforts need to be made to collect and analyze tumor tissues from these patients to search for molecular predictors of long-term benefit. A recent retrospective study of 164 patients receiving trastuzumab for advanced HER2-positive breast cancer discovered that prolonged trastuzumab treatment duration, a surrogate for trastuzumab benefit, was associated with hormone receptor-positive disease ($P = .032$) and a reduced likelihood of having received adjuvant trastuzumab ($P = .043$).

An important concern regarding the long-term use of trastuzumab is the cardiac tolerability of this approach. This drug is associated with cardiac toxicity, but most trastuzumab-related cardiac events are manageable and reversible, and they can be mitigated by careful patient selection and close monitoring. Moreover, patients who receive trastuzumab beyond progression (often for a prolonged period of time) have infrequent and primarily asymptomatic cardiac events.

For additional commentary about these topics and others, visit www.gotoper.com to access archived video of Dr. Swain and Dr. O'Shaughnessy from *Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer*.

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PER Pulse™ Recap
Treatment of Relapsed or Refractory HER2-Positive MBC

The online CME activity, *Oncology Consultations™: Management of HER2-Positive Metastatic Breast Cancer*, featured breast cancer experts Drs. Joyce O'Shaughnessy and Sandra Swain commenting on a case of a woman diagnosed with early-stage breast cancer in 1998 that metastasized 3 years after adjuvant chemotherapy and tamoxifen. They discussed the ongoing management of this patient, as well as current therapy options if that patient were being treated today. This third and final PER Pulse™ Recap from *Oncology Consultations™* focuses on the treatment of relapsed or refractory HER2-positive metastatic breast cancer (MBC).

The patient who was presented in the case study was treated with trastuzumab and chemotherapy in the first line for her HER2-positive MBC. After 4 years of combination therapy and 6 more of trastuzumab alone, the patient discontinued all treatment and developed a solitary liver metastasis within 12 months. She then initiated pertuzumab plus trastuzumab plus *nab*-paclitaxel and has tolerated this regimen well. As discussed in the first PER Pulse™ Recap of this *Oncology Consultations™*, dual inhibition with pertuzumab and trastuzumab is approved in the first-line setting for HER2-positive MBC, but this use of pertuzumab in the second line is off-label. Were this patient treated for newly diagnosed HER2-positive MBC today, she would likely have received a pertuzumab/trastuzumab-containing regimen upfront, and then moved to a different HER2-targeted regimen upon progression.

The value of continuing HER2 inhibition beyond progression has now been firmly established, and several such regimens can be used in the relapsed/refractory setting. The first of these to be approved was lapatinib plus capecitabine, a regimen indicated for trastuzumab-resistant disease based on a 4.0-month improvement in median time-to-progression (TTP) compared with capecitabine alone. Dr. O'Shaughnessy commented that with the recent approvals of pertuzumab, T-DM1 (ado-trastuzumab emtansine), and the new indication for lapatinib plus trastuzumab, she prefers to use lapatinib plus capecitabine primarily in patients with brain metastases. She further clarified that she tries to use it before patients undergo whole-brain radiation therapy (WBRT) because the LANDSCAPE trial demonstrated a much greater response rate in these patients than did the combination as reported by Nancy Lin and colleagues in patients after WBRT. Dr. Swain cautioned that the CEREBEL trial showed no advantage for using lapatinib over trastuzumab in patients with newly diagnosed brain metastases, a fact that has made her reconsider her use of lapatinib in this setting.

The antibody-drug conjugate T-DM1 earned its FDA approval for relapsed/refractory disease from the phase III EMILIA trial, which showed a 3.2-month improvement in median progression-free survival (PFS) and a 5.8-month improvement in median overall survival (OS) with T-DM1 compared with lapatinib/capecitabine in the relapsed/refractory advanced disease setting. Dr. Swain emphasized the excellent safety profile with T-DM1, saying that toxicities are minimal. Dr. O'Shaughnessy added that cardiac toxicity with T-DM1 is no different than would be expected from trastuzumab. The National Comprehensive Cancer Network (NCCN) breast cancer guidelines list T-DM1 as the preferred treatment option for taxane- and trastuzumab-exposed HER2-positive disease.

Other regimens recommended by the NCCN for relapsed/refractory HER2-positive MBC are combination regimens that include continuation of trastuzumab. Trastuzumab plus capecitabine is one example that has shown significantly greater response rates and prolonged TTP compared with capecitabine alone in this setting. Another is lapatinib plus trastuzumab, which has demonstrated both a significant but modest median PFS benefit (< 1 month; $P = .011$) and a significant and substantial median OS benefit (4.5 months; $P = .026$) compared with lapatinib alone. As might be expected, serious adverse events were more frequent in the combination arm, but the overall incidence of symptomatic cardiac events was low in both arms. Dr. O'Shaughnessy commented that she favors this treatment in later lines of therapy for patients with less tumor burden and more indolent disease because it lacks a cytotoxic agent.

The final regimen to be discussed for trastuzumab-resistant MBC is everolimus in combination with trastuzumab and vinorelbine, which was examined in the BOLERO-3 trial. The addition of everolimus produced a modest 1.2-month improvement in median PFS, and OS data are still immature. However, Dr. O'Shaughnessy was impressed with the improvement in PFS among patients with estrogen receptor-negative disease (HR = 0.65), so she has added it to her list

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