Pertuzumab plus trastuzumab and docetaxel in HER2-positive metastatic breast cancer

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The anti-HER2 monoclonal antibody trastuzumab works by binding to subdomain IV of the HER2 extracellular domain, thereby blocking HER2 cleavage; stimulating antibody-dependent, cell-mediated cytotoxicity; and preventing ligand-independent, HER2-mediated mitogenic signaling. Pertuzumab is an anti-HER2 monoclonal antibody that binds to subdomain II of the HER2 extracellular domain, preventing HER2 from dimerizing with other ligand-activated HER receptors; like trastuzumab, pertuzumab also stimulates antibody-dependent cell-mediated cytotoxicity. Pertuzumab's binding at a different HER2 epitope than trastuzumab represents a complementary mechanism of action that provides more comprehensive inhibition of HER2 signaling when the two agents are used together; the combination has been shown to produce greater antitumor activity than either agent alone in HER2-positive tumor models.[1]

Although the addition of trastuzumab to chemotherapy significantly improves survival in patients with HER2-positive metastatic breast cancer (MBC), most patients eventually progress. It is hoped that fuller inhibition of HER2 signaling with the combination of pertuzumab and trastuzumab might lead to greater improvement in survival.

The recently reported CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial showed that the addition of pertuzumab to trastuzumab and docetaxel significantly prolonged progression-free survival (PFS) in first-line treatment of patients with HER2-positive MBC.[2] An interim analysis showed a strong trend towards increased overall survival (OS) in the pertuzumab arm.

In this double-blind international trial, 808 patients were randomized to pertuzumab (402 patients) or placebo (406 patients) plus trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks) and docetaxel (75 mg/m^2 every 3 weeks). Pertuzumab was given as a loading dose of 840 mg, followed by 420 mg every 3 weeks. Study treatment was given until disease progression or development of toxic effects that could not be managed. The patients had a median age of 54 years in both groups and most were white (61% in pertuzumab group, 58% in

What's new, what's important

Development of HER2-targeted therapy has transformed the treatment of breast cancer. However, many patients still develop resistance to trastuzumab and other HER2-targeted agents, so it is important to find a new and better treatment for that subset of patients.

Previous studies of a combination of lapatinib and trastuzumab have shown promising results in the adjuvant, neoadjuvant, and metastatic settings; in studies of the combination in the neo-adjuvant setting, for example, patients have shown remarkable pathological response.

Pertuzumab and trastuzumab are both monoclonal antibodies that inhibit HER2-mediated signaling, but there are also differences between them: first, each agent recognizes unique extracellular epitopes, and second, the discrete binding site of pertuzumab induces structural aberrations that sterically hinder the process of homo- and heterodimerization, which trastuzumab does not. In effect, pertuzumab could inhibit HER2 signaling that has been initiated by ligand-activated HER1 or HER3 and thus provide even greater inhibition of HER2 than could trastuzumab. These unique features of the two agents allow for the possibility of their being synergistic when combined.

Findings from the CLEOPATRA study have shown that the combination of trastuzumab and pertuzumab clearly prolonged progression-free survival. Moreover, they did not show any increase in cardiac toxicity with the combination of the two HER2-targeted agents. The incidence of diarrhea and febrile neutropenia as side effects was higher in patients in the pertuzumab group compared with those in the trastuzumab group. So overall, this is an exciting development for patients with HER2-positive metastatic breast cancer.

The ongoing APHINITY trial will give us more data about the role of this combination in early breast cancer and long-term toxicity.

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control group). Similar proportions of patients in the pertuzumab and control groups had ECOG performance status of 0 (68% and 61%, respectively), had visceral disease at baseline (78% and 78%), and were estrogen receptor- and progesterone receptor-negative (53% and 48%). Similar proportions of pertuzumab and control patients had HER2 status of 3+ on immunohistochemistry (87% and 91%) and were HER2-positive on fluorescence in situ hybridization (95.5% and 94%). Previous adjuvant or neoadjuvant chemotherapy had been received by 46% of patients in the pertuzumab arm (anthracycline in 37%, hormone in 26%, taxane in 23%, and trastuzumab in 12%) and by 47% of patients in the control arm (anthracycline in 40%, hormone in 24%, taxane in 23%, and trastuzumab in 10%).

Independently assessed median PFS, the primary endpoint of the trial, was 18.5 months in the pertuzumab group and 12.4 months in the control group, representing a 38% reduction in risk for progression or death (hazard ratio [HR], 0.62; $P < .001$). The benefit of the addition of pertuzumab in PFS was observed across all predefined subgroups. Among the 88 patients with previous exposure to trastuzumab as part of adjuvant or neoadjuvant chemotherapy, the median PFS was 16.9 months in the pertuzumab group and 10.4 months in the control group (HR, 0.62; 95% confidence interval [CI] 0.35-1.07). Among the 288 patients who had received adjuvant or neoadjuvant chemotherapy not including trastuzumab, median PFS was 21.6 months in the pertuzumab group and 12.6 months in the control group (HR, 0.60; 95% CI 0.43-0.83). Investigator-assessed PFS also showed a significant 35% reduction in risk of progression or death (HR, 0.65; $P < .001$).

An interim analysis of OS was performed when 165 events had occurred (43% of the prespecified total number for the final analysis), at a median follow-up of 19.3 months in both arms. There was a lower incidence of death in the pertuzumab group (17.2% vs 23.6%, respectively), representing a 36% reduction in risk for death with pertuzumab (HR, 0.64; $P = .005$). Although this indicates a strong trend toward a significant OS benefit in the pertuzumab group, the difference did not meet the stopping boundary for the interim analysis (HR, 0.603; P .0012). Objective response rates were 80.2% in the pertuzumab group and 69.3% in the control group ($P = .001$).

Patients in both groups received a median of 15 study treatment cycles and both groups received a median of 8 cycles of docetaxel. The doses of trastuzumab and pertuzumab could not be changed, but the docetaxel dose could be increased to 100 mg/m^2 if side-effects permitted and decreased to 55 mg/m^2 or from 100 mg/m^2 back to 75 mg/m^2 depending on toxic effects. The median dose intensities of docetaxel were 24.6 mg/m^2 per week in the pertuzumab group and 24.8 mg/m^2 per week in the control group. More patients in the control group than in the pertuzumab group had an increase in docetaxel dose to 100 mg/m^2 for at least 1 cycle (15.4% vs 11.8%, respectively).

For adverse events of any grade, rates were at least 5% greater in the pertuzumab group than in the control group for diarrhea (67% vs 46%, respectively), rash (34% vs 24%), mucosal inflammation (28% vs 20%), febrile neutropenia (14% vs 8%), and dry skin (11% vs 4%). For adverse events of grade 3 or higher, rates were at least 2% greater in the pertuzumab group for neutropenia (49% vs 46%), febrile neutropenia (14% vs 8%), and diarrhea (8% vs 5%). The incidence of grade 3 or worse neutropenia in

How I treat HER2-positive metastatic breast cancer

Treating advanced HER2-positive breast cancer is certainly more gratifying in the era of HER2-targeted therapy, when survival times have improved significantly. The pivotal trial reported by Slamon et al (*N Engl J Med.* 2001;344[11]:783-792) underestimates the true benefit of trastuzumab that we see in the clinic because we now use sequential therapies that continue HER2 blockade, which was not the case for patients who were on the early trials before trastuzumab was approved.

As an initial treatment for HER2-positive breast cancer, I take the patient's hormone receptor status into consideration and will use hormonal therapy with either trastuzumab or lapatinib for lower burden disease as the initial treatment. Although patients generally will need to move on to chemotherapy, some actually enjoy a long time of progression-free survival without chemotherapy effects. When I use chemotherapy with trastuzumab, I tend to use single chemotherapy agents—mostly weekly paclitaxel, as well as vinorelbine and capecitabine as an initial or subsequent therapy; the exact sequence is dictated by patient symptoms, patient preference, and previous therapies.

For very aggressive disease, I use weekly paclitaxel and carboplatin initially. I also use lapatinib at either initial or subsequent progression, although I am more restrictive with the chemotherapy partner—using mostly capecitabine and not paclitaxel because of the toxicity. Lately, I have been using trastuzumab and lapatinib together earlier in the "rotation." For patients who develop brain metastases, I use local therapy (surgery when feasible, followed by stereotactic or whole brain radiation), but I do not change systemic therapy unless they are exhibiting new or progressive systemic disease. I slightly favor lapatinib for brain metastases based on the scant data pointing to better CNS penetration, but there are data to support a benefit from trastuzumab as well.

— Debu Tripathy, MD

patients from Asia was 26% in the pertuzumab group and 12% in the control group; in all other geographic regions, the incidence was 10% or less in both groups. More control group patients had left ventricular systolic dysfunction of any grade (8.3% vs 4.4%) or of grade 3 or higher (2.8% vs 1.2%). In patients with postbaseline left ventricular ejection fraction measurements, more patients in the control group had decreases of 10% or more that resulted in an ejection fraction of less than 50% (6.6% vs 3.8%).

Most of the deaths that occurred during the study were related to disease progression. A similar proportion of pertuzumab patients and control patients died as a result of adverse events (2.0% vs 2.5%, respectively), with infection being the most common cause of death due to an adverse event.

References

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