POINT: HER2-Targeted Combinations in Advanced HER2-Positive Breast Cancer

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We acknowledge that the “more is better” approach may not always hold true. For example, preclinical data provided a rationale for combining pertuzumab with T-DM1, but recent reports suggest that this strategy may not prove more effective than single-agent T-DM1 therapy in the clinic.

A Paradigm Shift From a Dogma of the Cytotoxic Era

The primary goals when treating patients with metastatic breast cancer are to improve both duration and quality of life. With cytotoxic chemotherapy, this is typically achieved by using single agents sequentially (rather than combination regimens), switching therapies in the face of disease progression or prohibitive toxicity. This approach is supported by clinical trial data showing that chemotherapy doublets enhance neither the duration nor the quality of life compared with sequential single agents.[1,2] Combination therapy is more likely to be associated with drug toxicity, without clear evidence of benefit.

We argue that the same principle does not hold true when using targeted agents for advanced human epidermal growth factor receptor (HER) 2-positive breast cancer. Rather, there is often a strong case for combining the anti-HER2 antibody trastuzumab with another HER2-directed therapy. Unlike with chemotherapy, the efficacy-vs-toxicity trade-off often favors combination approaches in the setting of HER2-positive disease.

The notion that combining anti-HER2 therapies might be particularly effective stems from the fact that each of these agents targets the HER2 signaling pathway differently. Trastuzumab interferes with ligand-independent HER2-HER3 interactions and prevents cleavage of HER2 at the membrane, whereas pertuzumab prevents ligand-dependent HER2-HER3 interactions. In contrast, lapatinib inhibits the function of the epidermal growth factor receptor (EGFR) and HER2 kinases.[3] Both antibodies, but not lapatinib, also invoke antibody-dependent cell-mediated cytotoxicity (ADCC) against tumor cells.

Trastuzumab + Pertuzumab

Striking preclinical and clinical data support use of the trastuzumab + pertuzumab combination. HER2-HER3 heterodimers are the dominant mediators of signaling in HER2-positive breast cancers[4]; through enhanced prevention of HER2-HER3 interactions, trastuzumab and pertuzumab act synergistically against tumor cells in vitro.[5]

In keeping with laboratory data, results of the BO17929 clinical trial suggest synergistic antitumor activity when trastuzumab and pertuzumab are combined. In this nonrandomized study, one cohort of patients whose metastatic disease was progressing on trastuzumab was treated with pertuzumab alone, yielding an overall response rate (ORR) of only 3%. When these patients then switched to the trastuzumab + pertuzumab combination (ie, after their disease had progressed on both trastuzumab and pertuzumab used individually), an ORR of 18% was observed.[6] The notable ORR with trastuzumab + pertuzumab in patients in whom each agent used individually had failed speaks to the benefit of using these agents in combination.

Further data supporting use of the trastuzumab + pertuzumab combination has come from the randomized phase III Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study.[7] Although this first-line metastatic trial did not specifically compare combination vs sequential anti-HER2 therapy, the addition of pertuzumab to a docetaxel/trastuzumab backbone yielded an unprecedented 15-month improvement in overall survival (OS). This improvement came at the cost of extra toxicity (diarrhea, mucositis, rash, and febrile neutropenia), but the magnitude of the benefit and relatively modest toxicity have cemented the position of trastuzumab + pertuzumab as an...
integral component of first-line therapy for advanced HER2-positive breast cancer.

**Trastuzumab + Lapatinib**

The other clinically relevant combination is trastuzumab + lapatinib. Lapatinib is often active against trastuzumab-resistant cell lines,[8] and the trastuzumab + lapatinib combination can act synergistically in vitro.[9] This synergy might arise because lapatinib stabilizes HER2 at the cell membrane, potentiating the effects of trastuzumab and enhancing signal inhibition and apoptosis.[9,10]

Trial data also support use of the trastuzumab + lapatinib combination. In the randomized EGF104900 study, trastuzumab + lapatinib prolonged OS by more than 4 months compared with lapatinib monotherapy in a cohort of heavily pretreated, trastuzumab-resistant patients.[11] Further, trastuzumab + lapatinib was associated with a trend towards improved quality of life,[12] partly reflecting the nonoverlapping toxicities of these agents. Whether the survival benefit seen was due to synergistic inhibition of HER2 signaling or to the persistent influence of trastuzumab-related ADCC in the trastuzumab + lapatinib arm is unknown.

In summary, targeted anti-HER2 agents can act synergistically, and when used in the trastuzumab + pertuzumab or trastuzumab + lapatinib combinations, can improve patient outcomes at the price of manageable toxicity. Indeed, in clinical practice, we would not consider using pertuzumab without concomitant trastuzumab, and would only use lapatinib in conjunction with trastuzumab and/or chemotherapy, but never as a single agent.

We acknowledge that the “more is better” approach may not always hold true. For example, preclinical data provided a rationale for combining pertuzumab with the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1),[13] but recent reports suggest that this strategy may not prove more effective than single-agent T-DM1 therapy in the clinic.[14] This discordance between preclinical and clinical data requires further investigation, and reminds us that each new combination regimen must be assessed on its individual merits.

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