Neoadjuvant Chemo to Refine Risk in HER2-Positive Breast Cancer

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Neoadjuvant chemotherapy was originally employed in breast cancer patients who presented with inoperable disease in order to render them operable candidates. When the benefit from adjuvant chemotherapy was demonstrated in early-stage breast cancer, the use of neoadjuvant chemotherapy expanded to include patients with operable disease. Several randomized clinical trials have shown similar benefits from chemotherapy when used either in the neoadjuvant or adjuvant settings (Lancet Oncol 2018;19:27-39; J Natl Cancer Inst 2005;97:188-194; J Clin Oncol 2008;26:778-785). These trials also demonstrated increasing rates of clinical tumor response, which in turn provided the potential for surgical de-escalation in the breast and axilla with considerable

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How Light Therapy Can Help With Oral Mucositis Management

By SARAH DIGIULIO

Oral mucositis is a common and sometimes extremely debilitating side effect associated with chemotherapy and radiation treatments. The lesions and sores not only cause pain and discomfort, but they can compromise nutrition and oral hygiene, increase risk of infection, and limit a patient’s dose (and thereby efficacy) of cancer treatment (Dent Clin North Am 2008; 52(1):61-77).

One therapy that does help is photobiomodulation (sometimes referred to as low-level light therapy or low-level laser therapy). Researchers began studying the cell-repairing effects of photobiomodulation therapy in the 1970s. And studies began to show the modality’s effectiveness for helping patients with oral mucositis as early as the 1990s.

Previous guidelines from MASCC/ISOO published in 2014 recommended the use of photobiomodulation therapy to help manage oral mucositis in patients with cancer, but those recommendations were based on low-level evidence and limited protocols were recommended (Cancer 2014;120:1453-1461).

Now, updated MASCC/ISOO guidelines published in the journal Supportive Care in Cancer in July, have expanded the

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Maximizing Benefits of Neoadjuvant Chemo

Although the early benefits from neoadjuvant chemotherapy focused on loco-regional therapy de-escalation, more recently, interest developed in using this approach for also tailoring adjuvant systemic therapy after neoadjuvant chemotherapy. The development of multiple active chemotherapy drugs and regimens for early-stage breast cancer has allowed us to test two hypotheses in the neoadjuvant setting.

The first hypothesis postulates that increased pCR rates with more active regimens will continue to correlate with improved outcomes. The second hypothesis postulates that tumors that do not respond or partially respond to the original neoadjuvant regimen may respond to other active non-cross resistant regimens used either as neoadjuvant or post-neoadjuvant therapy (i.e., chemotherapy resistance is regimen- or drug-specific). Based on this second hypothesis, presence of residual disease after neoadjuvant chemotherapy evolved from the challenging clinical situation of realizing the increased residual risk for recurrence, to an opportunity for intervention with non-cross resistant regimens in order to reduce that risk. Thus, the setting of residual disease following neoadjuvant chemotherapy became a fertile ground for clinical trials that allow for enrollment of high-risk patients with tumors proven to be resistant to existing therapies, justifying the use of novel experimental approaches.

Since these novel treatments are given as adjuvant therapy and the trials employ standard clinical endpoints, they are considered by the FDA for regulatory approval. The high event rate allows for trials with smaller sample size than the original adjuvant therapy trials and results can be obtained with shorter follow up. In addition, obtaining translational research data from the residual tumor that has proven to be resistant to the original neoadjuvant therapy regimen can lead to better understanding of resistance biomarkers and pathways.

The KATHERINE Trial

Based on the above rationale, the KATHERINE trial was a phase III, open-label clinical trial in patients with HER2-positive early breast cancer who were found to have residual invasive disease in the breast or axilla after receiving neoadjuvant chemotherapy containing a taxane-based regimen plus trastuzumab (with or without anthracyclines) (N Engl J Med 2019;380:617-628).

Patients were randomly assigned to receive adjuvant trastuzumab emtansine (T-DM1) or trastuzumab for 14 cycles. T-DM1 is an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine, a maytansine derivative and microtubule inhibitor (Cancer Res 2008;68:9280-9290). T-DM1 retains trastuzumab activity while providing intracellular delivery of emtansine to HER2-overexpressing cells (Breast Cancer Res Treat 2011;128:347-356).

In two phase III trials in patients with HER2-positive advanced breast cancer who had previously received HER2-targeted therapy including trastuzumab and chemotherapy, T-DM1 showed superior efficacy and a favorable risk–benefit profile compared with capetitabine/lapatinib or treatment of physician’s choice (N Engl J Med 2012;367:1783-1791; Lancet Oncol 2014;15:689-699; Lancet Oncol 2017;18:732-742; Lancet Oncol 2017;18:743-754). T-DM1 is approved for use in patients with HER2-positive metastatic breast cancer who have previously received treatment with trastuzumab and a taxane. Administration of 17 cycles of T-DM1 after an anthracycline regimen was found to be feasible and not associated with unacceptable toxicity in a phase II trial in patients with HER2-positive early breast cancer (J Clin Oncol 2015;33:1136-1142).

The primary aim of the KATHERINE trial was to determine whether adjuvant T-DM1 would be superior to adjuvant trastuzumab in improving invasive disease-free survival (defined as freedom from ipsilateral invasive breast tumor recurrence, ipsilateral loco-regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause).

Eligible patients had histologically confirmed, HER2-positive, non-metastatic, invasive primary breast cancer at presentation (cT1-4, cN0-3, M0 excluding clinical stage T1a-bN0M0) and residual invasive disease in the surgical specimen of the breast or axillary lymph nodes after completion of taxane-based neoadjuvant chemotherapy plus trastuzumab. HER2 status was centrally confirmed in the pre-treatment biopsy samples and, if not available, in the residual tumor from the surgical specimen. Patients had to have completed at least 6 cycles of a conventional neoadjuvant chemotherapy regimen containing a minimum of 9 weeks of taxane-based therapy and 9 weeks of trastuzumab. Anthracyclines and alkylating agents were permitted according to local standards, as were additional HER2-targeted agents. Eligible patients were randomized within 12 weeks after surgery, to receive T-DM1 (3.6 mg/kg) or trastuzumab (6 mg/kg) intravenously every 3 weeks for 14 cycles. A loading dose of 8 mg/kg of trastuzumab was administered if more than 6 weeks had elapsed since the preceding dose of trastuzumab. Patients who discontinued T-DM1 early because of toxic effects could complete 14 cycles of trial treatment with trastuzumab at the discretion of the investigator. Radiation therapy and endocrine therapy were administered according to institutional standards and the trial protocol.

The statistical design of the trial provided 80 percent power to detect a hazard ratio of 0.75 with a two-sided significance level of 5 percent for the primary analysis. A single interim analysis of invasive disease-free survival (IDFS) was planned when approximately two-thirds of the projected invasive-disease events had occurred, with a P value of <0.0124 for an efficacy stopping boundary or an observed hazard ratio of < 0.732. The results of the interim analysis crossed the early stopping boundary for benefit with T-DM1 and were subsequently presented at the 2018 San Antonio Breast Cancer Symposium and simultaneously published in the New England Journal of Medicine (2019;380:617-628).

From 4/13 through 12/15, 1,486 patients were randomized to T-DM1 or trastuzumab (743 patients per group). Baseline patient, tumor, and treatment characteristics were well-balanced between the two treatment groups. Hormone-receptor–positive disease was present in 72.3 percent

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of the patients. The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen, and another HER2-targeted agent in addition to trastuzumab was used as a component of neoadjuvant therapy in 19.5% of patients.

At the interim analysis, an iDFS event had occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). iDFS was significantly higher in the T-DM1 group versus the trastuzumab group (HR for iDFS event: 0.50; 95% CI, 0.39-0.64; P<0.001). The estimated 3-year iDFS was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. A subgroup analysis of iDFS revealed a consistent benefit of T-DM1 across stratification cohorts and other subgroups, including patients with hormone-receptor–positive or hormone-receptor–negative disease, patients with positive or negative pathological nodal status after neoadjuvant therapy, patients with either no residual invasive primary disease or residual primary disease of 1 cm or less in the breast, as well as patients who received neoadjuvant chemotherapy plus trastuzumab and those who received neoadjuvant chemotherapy plus dual anti-HER2 therapy (over 93% of those received trastuzumab plus pertuzumab). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group.

The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone. All 14 cycles of assigned therapy were completed in 71.4% of patients in the T-DM1 group and in 81.0% of patients in the trastuzumab group. Serious adverse events occurred in 12.7% of patients who received T-DM1 and 8.1% of patients who received trastuzumab. The most common adverse events of ≥ grade 3 were decreased platelet count (5.7%) and hypertension (2.0%) in the T-DM1 group and hypertension (in 1.2%) and radiation-related skin injury (in 1.0%) in the trastuzumab group. One patient in the T-DM1 group who had a decreased platelet count died from an intracranial hemorrhage that occurred after a fall.

Based on the KATHERINE results, in May 2019, the FDA approved T-DM1 for adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. This is the first time an antibody-drug conjugate has been shown to be successful in treating early-stage breast cancer.

The results of the KATHERINE trial provide new options in the treatment of HER2-positive patients with residual invasive disease after neoadjuvant chemotherapy. These results further validate the neoadjuvant approach for such patients. With this approach, one can better tailor loco-regional and systemic therapy and improve outcomes, an opportunity that is lost if patients are treated with surgery first followed by adjuvant chemotherapy plus anti-HER-2 therapy (Lancet Oncol 2019;20:e390-e396).