Further Progress for Patients with Breast Cancer

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Substantial progress has been made over the past 50 years in the evaluation and treatment of patients with breast cancer, leading to a nearly 40% decrease in mortality from this disease and associated reductions in complications of treatment. This progress has occurred with the understanding that breast cancer is not one but several diseases with biologically driven subtypes. Each of these subtypes is amenable to different treatment strategies, so that a personalized-medicine approach is possible in the treatment of patients with breast cancer.

For example, endocrine treatment in women with estrogen-receptor–positive, but not estrogen-receptor–negative, breast cancer has led to considerable improvement in survival while avoiding toxic effects in patients who would not benefit. Similarly, identification of overexpression of its protein product, human epidermal growth factor receptor 2 (HER2), or both has produced remarkable results. The humanized monoclonal antibody trastuzumab, which is directed against HER2, is highly effective in patients with metastatic HER2-positive breast cancer, and it has decreased the rate of distant recurrence and death by nearly one half among patients with early-stage disease. In addition to trastuzumab, several other anti-HER2 agents, including pertuzumab, lapatinib, and neratinib, have been introduced into the clinic.

Yet another agent, trastuzumab emtansine, designated T-DM1, consists of an antitubulin chemotherapeutic agent, emtansine, which is chemically linked to trastuzumab. T-DM1 has impressive activity against HER2-positive metastatic breast cancer, even in patients with cancer that had previously progressed with trastuzumab-based therapy, and it has serious but mainly reversible toxic effects. Results of studies of T-DM1 suggest that it behaves as a Trojan horse, delivering emtansine only to HER2-expressing cells and mostly sparing patients from the considerable toxic effects seen with the predecessor of emtansine, maytansine, when used as a single agent.

Successful neoadjuvant treatment of patients with metastatic breast cancer frequently portends even greater benefit in the adjuvant setting. Indeed, tests of most of the new anti-HER2 therapies as preoperative (or neoadjuvant) therapy in patients with early disease have induced substantial tumor shrinkage. However, enigmatically, results of classic trials of adjuvant lapatinib and pertuzumab, either alone or in combination with trastuzumab, have been disappointing with regard to clinically meaningful end points such as a reduction in rates of distant recurrence or death.

In this issue of the Journal, von Minckwitz et al. report a remarkable benefit in women with stage I to III HER2-positive breast cancer. All patients enrolled in this trial had residual disease after receiving neoadjuvant chemotherapy plus trastuzumab (and, in a minority, after receiving pertuzumab) and were randomly assigned to postoperative T-DM1 or trastuzumab for the succeeding 42 weeks. A significant reduction of nearly one half in the risk of invasive events (invasive breast cancer or death), including the risk of distant recurrence, was observed. Overall, there was an absolute improvement of 11.3 percentage points in the rate of invasive disease–free survival. Even though the trial was underpowered to detect a significant reduction in mortality, the hazard ratio for death was similar to the hazard ratio for distant recurrence (0.7 and 0.6, respectively).

These results are impressive and clinically meaningful. However, success does not come without a price. More serious adverse events occurred in patients who received T-DM1 than in those who received trastuzumab (12.7% vs.
8.1%), and more patients discontinued T-DM1 than trastuzumab (18.0% vs. 2.1%) before the completion of the anticipated 14 postsurgical cycles. One of the five deaths among patients who did not have disease recurrence occurred in a patient who had an intracranial hemorrhage after a fall associated with T-DM1–induced thrombocytopenia (Table S2 in the Supplementary Appendix of the article, available at NEJM.org).

Like any well-designed and well-conducted trial, this one also raises many questions. Could single-agent T-DM1 be used as the sole therapy instead of combination chemotherapy with trastuzumab for many patients with HER2-positive disease? At least two trials have suggested that rates of pathological complete response, and even disease-free survival, are similar with neo-adjuvant T-DM1 and trastuzumab.10,13 Could the use of adjuvant anthracyclines be reduced? Although most patients in the current trial received anthracyclines, the availability of yet another opportunity to improve long-term outcomes. Caveat emptor: doctors and patients need to be aware that the side effects of this regimen are more common than with trastuzumab alone, and occasional severe toxic effects need to be considered. Therefore, T-DM1 should not be used in patients with a pathological complete response or in those with stage I disease; these patients have a very favorable outcome with adjuvant paclitaxel and trastuzumab alone.15 Nonetheless, this trial is one more step toward personalized medicine and reduced mortality among patients with early-stage breast cancer.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Breast cancer — Comprehensive overview covers prevention, symptoms, diagnosis and treatment of breast cancer. If your doctor has assessed your family history and determined that you have other factors, such as a precancerous breast condition, that increase your risk of breast cancer, you may discuss options to reduce your risk, such as: Preventive medications (chemoprevention). Estrogen-blocking medications, such as selective estrogen receptor modulators and aromatase inhibitors, reduce the risk of breast cancer in women with a high risk of the disease. These medications carry a risk of side effects, so doctors reserve these medications for women who have a very high risk of breast cancer. Of the 268,000 patients in whom breast cancer is diagnosed in the United States each year, approximately 32% have positive lymph nodes at the time of diagnosis. Suspicious lymph nodes are often detected on clinical breast examination, mammography, or ultrasonography. The diagnosis of positive lymph nodes, however, requires fine-needle aspiration or a core needle biopsy. A simplified schema of my approach to patients with breast cancer who present with biopsy-proven positive nodes is shown in the Figure. Metastatic Workup. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072-1078. Breast cancer treatments can be tough but be clothed in strength, dignity and a little laughter whenever you can. In addition, Lapatinib (Tykerb®) is used as part of combined therapy in patients with HER2-positive breast cancer that has progressed after trastuzumab (Herceptin®) treatment. PARP Inhibitors — olaparib (Lynparza®). The enzyme, poly ADP ribose polymerase (PARP), is used by cells to repair DNA damage. Inhibitors of PARP block DNA repair and may cause rapidly dividing cells, such as cancer cells, to die. For patients with high-grade DCIS, post-excision radiotherapy may be an important treatment for reducing the risk of breast disease in the same breast. Radiotherapy, that word is scary. It’s the thought of losing your hair and being very sick.