EDITORIALS

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.[1] This progress has occurred with the understanding that breast cancer is not one but several diseases with biologically driven subtypes.[2] 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.[3] Similarly, identification of amplification of *ERBB2*, identification of overexpression of its protein product, human epidermal growth factor receptor 2 (HER2), or both has produced remarkable results.[4] 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.[5] 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,[6] 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.[7]

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.[8-11]

In this issue of the *Journal*, von Minckwitz et al.[12] 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 neoadjuvant 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 active agent in early-stage breast cancer could lead to less use of anthracyclines, which would avoid the small but real risk of congestive heart failure and hematologic cancers. What are the implications of the results of this trial for anti-HER2 agents other than trastuzumab? Postoperative T-DM1 might eliminate the use of neratinib, which has produced a significant but very modest absolute reduction in benefits as compared with placebo after 12 months of trastuzumab.[14] These questions all warrant careful consideration and need to be addressed in subsequent trials.

In conclusion, the trial by von Minckwitz and colleagues is a game changer. It suggests that neoadjuvant chemotherapy with trastuzumab, with or without pertuzumab, is the standard of care for patients with newly diagnosed HER2-positive breast cancer, especially those with stage II or III disease. This approach has the ability to reduce the extent of local treatment. More important, it will guide postoperative systemic therapy. If patients do not have a pathological complete response with such a regimen, postoperative treatment with T-DM1 offers a major 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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