Perspective

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

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New drugs for breast cancer have historically been approved first for patients with metastatic disease who have few remaining options for systemic treatment. Approval for an adjuvant indication occurs years later, after large, randomized trials with prolonged follow-up have been conducted in patients with early-stage disease. Recently, neoadjuvant trials have introduced new drugs preoperatively in patients with localized breast cancer. Such treatment aims to render locally advanced cancers operable, facilitate breast-conserving surgery, and ultimately improve survival. The rate of pathological complete response — absence of residual invasive cancer on pathological evaluation of resected breast specimens and lymph nodes after preoperative therapy — has been used as the primary end point in many neoadjuvant trials.

Promising investigational drugs should be incorporated into standard treatment for early-stage breast cancer as rapidly as possible to provide the greatest benefit to the most patients. But this goal must be weighed against the limited safety data available for new drugs when they are used in patients with curable cancer and uncertainty about whether improvement in pathological complete response will predict improvements in long-term disease-free or overall survival.

The uncertainties regarding the risks and benefits of new neoadjuvant drugs may be managed by enrolling patients who have the greatest risk of recurrence with existing therapies and are likely to benefit the most. Although modern cytotoxic regimens have reduced 10-year breast-cancer–related mortality by approximately one third, certain patients with early-stage breast cancer, particularly those with high-grade tumors that are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (i.e., triple negative), remain at substantial risk for distant metastatic disease and death.

Randomized neoadjuvant trials suggest that a pathological complete response may predict disease-free or overall survival among patients with early-stage breast cancer who are treated with preoperative systemic therapy. A Cochrane meta-analysis of 5500 patients enrolled in 14 randomized trials comparing preoperative with postoperative chemotherapy showed that the risk of death among patients who had a pathological complete response was about half that of patients with residual tumor at the time of surgery.[1]

In the United States, regular approval of a new drug requires adequate, well-controlled trials demonstrating clinical benefit, which is generally defined in early-stage breast cancer as an improvement in disease-free or overall survival. Alternatively, the Food and Drug Administration (FDA) may grant accelerated approval on the basis of a surrogate end point that is "reasonably likely to predict clinical benefit." For neoadjuvant breast-cancer treatment, we propose that the rate of pathological complete response be used as this surrogate.[2] After accelerated approval, demonstration of an improvement in disease-free or overall survival would be required; the indication may be withdrawn from product labeling if confirmatory trials have not shown clinical benefit.

For regulatory purposes, neoadjuvant trials evaluating a new drug with limited safety data should enroll patients with high-risk features and exclude those with ER- or PR-positive tumors lacking these characteristics. Patients may be classified as having a high risk of recurrence on the basis of conventional histologic features or appropriately validated genomic measures. The highest rates of pathological complete response have generally been observed among patients with high-grade ER-

and PR-negative tumors and those with HER2-positive tumors.[3] Although patients with triple-negative breast cancer have an increased risk of recurrence, if a pathological complete response is achieved, the likelihood of survival may be similar to that among patients with more prognostically favorable subtypes.[3,4] Patients with ER- and PR-positive tumors are less likely to have a pathological complete response to neoadjuvant therapy and more likely to live longer with available therapy; pathological complete response is thus unlikely to predict clinical benefit in this subgroup.[3] We discourage enrollment of patients with low-grade ER- and PR-positive tumors into neoadjuvant trials conducted with regulatory intent.

A large, randomized trial of neoadjuvant breast-cancer treatment using an add-on design — studying a standard adjuvant regimen with or without the new drug, all delivered preoperatively — could be used for an accelerated-approval submission. This single randomized trial, if adequately powered, could both support accelerated approval on the basis of substantial improvement in the pathological complete response rate and, with further follow-up, provide data on potential improvements in disease-free and overall survival to establish clinical benefit. Use of postoperative systemic therapy should be avoided but if needed (e.g., for completion of a year of adjuvant trastuzumab for HER2-positive breast cancer) should be consistent in both treatment groups to avoid confounding interpretations of disease-free and overall survival. Demonstration, with mature data, of a clinically and statistically significant improvement in disease-free or overall survival would fulfill the requirements for regular approval and permit continued marketing of the drug for neoadjuvant use in breast cancer.

At the time of accelerated approval, characterization of long-term toxic effects may be incomplete, and uncommon adverse events may not be recognized or fully described. A comprehensive safety assessment is critical in evaluating the benefits of neoadjuvant therapy for patients with early-stage breast cancer, among whom long-term survival is common and may result solely from local therapy. There is a risk that a drug approved in this way could be marketed for a prolonged period, exposing many patients with curable disease and potentially normal longevity to the risks posed by an ultimately ineffective therapy. To mitigate this risk, randomized neoadjuvant trials conducted with marketing intent should be limited to subpopulations at high risk for recurrence despite optimal local and systemic therapies, and confirmatory trials should be ongoing at the time of accelerated approval.

The trial design described above would isolate the new drug's effect and provide a larger body of safety data at the time of accelerated approval. Continued follow-up in the same trial would provide essential information on late or cumulative toxic effects, as well as mature efficacy outcome data, far more quickly than a subsequent adjuvant trial could do and would hasten clarification of the relationship between the pathological complete response rate and survival. For drugs with more extensive prior use in breast cancer or evidence of unprecedented efficacy, or for drugs being studied in ongoing randomized adjuvant trials, alternative approaches may be acceptable and should be discussed with the FDA.

The proposed magnitude of the difference between treatment groups in the pathological complete response rate should be prespecified and have a high likelihood of translating into a meaningful improvement in disease-free or overall survival; the sample size required to demonstrate a significant difference in survival may be substantially larger than that needed to demonstrate a significant difference in pathological complete response rates. Statistical analyses should use the full intention-to-treat population. Since distant metastatic disease will develop in some patients with a pathological complete response, small absolute improvements probably will not have a meaningful effect on long-term clinical benefit; substantial improvements may be needed to improve disease-free or overall survival. For example, in a neoadjuvant trial of chemotherapy with or without trastuzumab, the group that received trastuzumab had a near doubling of the pathological complete response rate (39% vs. 20%) and a 3-year disease-free survival rate of 71%, as compared with 56% in the other treatment group.[5] Similarly, adjuvant trials of chemotherapy with or without trastuzumab have demonstrated an approximately 50% relative (12% absolute) improvement in disease-free survival when trastuzumab was added.[6]

Despite the promise of pathological complete response as an end point for accelerated approval, unresolved issues remain, including the definition of such a response that optimally predicts long-term clinical outcomes, the intrinsic breast-cancer subtypes most likely to show such a response, and the magnitude of improvement needed to produce meaningful improvements in disease-free and overall survival. In collaboration with international investigators, the FDA is conducting a meta-analysis using primary-source data from more than 12,000 patients enrolled in randomized neoadjuvant trials, aiming to identify those in whom a pathological complete response is most likely to predict clinical benefit by correlating this end point with disease-free and overall survival in intrinsic breast-cancer subtypes.

The FDA has released a draft Guidance to Industry,[2] outlining a pathway to accelerated approval for neoadjuvant breast-cancer therapies and seeking public comments on the use of pathological complete response as an end point for accelerated approval.

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

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