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Virginia G. Kaklamani, MD, DSc

Virginia G. Kaklamani, MD, DSc, is Professor of Medicine and Leader of the Breast Oncology Program, CTRC, at the University of Texas Health Science Center in San Antonio.

Is the Preoperative Setting an Appropriate Platform for Drug Approval in Breast Cancer?

Virginia G. Kaklamani, MD, DSc, and William J. Gradishar, MD

The pathway for new drug approval is a long process requiring significant financial and patient-related resources. Historically, companies seeking new drug approval had to show a clearly favorable therapeutic profile with a relatively safe toxicity index. Phase III clinical trials involving a large number of patients and long follow-up time have been the preferred clinical trial designs supporting new drug approval in the early-stage setting. This process, however, has been criticized for the amount of resources (both patients and cost) and time needed and the delay in giving life-saving drugs to patients with cancer.

Recently, the FDA allowed for accelerated drug approval in cases in which neoadjuvant clinical trials show a significant improvement in pathologic complete response, and full approval is pending long-term efficacy data. This led to the approval of pertuzumab, a monoclonal antibody against HER2, in combination with trastuzumab in HER2-positive early-stage breast cancer. Recently, lapatinib was also tested in the preoperative setting with results similar to those of pertuzumab. Yet the phase III data were negative, calling into question the validity of using neoadjuvant clinical trials as the pathway to drug approval. This commentary discusses the evidence behind the use of neoadjuvant clinical trials as a platform for approving medications in the adjuvant setting.

In breast cancer, preoperative systemic therapy (neoadjuvant therapy) is given before definitive surgery. Preoperative systemic therapy has been used in patients with large tumors or tumors with direct extension to the skin or surrounding structures, which may not be amenable to primary resection.[1] Preoperative systemic therapy has also been used to convert a potential mastectomy to a segmental mastectomy. A potential benefit of preoperative therapy is the ability to evaluate the efficacy of the treatment at the time of surgery[1]

In 2012, the FDA released guidelines for accelerated drug approval in early-stage breast cancer. In summary, these guidelines noted that, "The 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 pathologic complete response (pCR) be used as this surrogate.[2] In an accompanying article, Prowell and Pazdur[2] from the FDA suggested that the design of these neoadjuvant clinical trials should be used for breast cancer subtypes with clear data on the importance of pCR. Furthermore, they suggested that "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." Finally, they stress that long-term outcomes, such as disease-free survival (DFS) and overall survival (OS), are needed to fulfill the requirements for regular approval of the drug.

Are Long-Term Outcomes Different Between Neoadjuvant and Adjuvant Chemotherapy?

The NSASBP B18 was a study with the primary goal of determining whether preoperative chemotherapy would result in improved OS and DFS relative to the same chemotherapy administered postoperatively.[3] Patients with operable, palpable, biopsy-proven early-stage breast cancer were randomized to receive either surgery (lumpectomy and axillary lymph node dissection or modified radical mastectomy) followed by 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) (AC) chemotherapy every 21 days, or the same chemotherapy followed by surgery. Secondary goals were to evaluate the response of the primary breast tumor and involved lymph nodes to preoperative chemotherapy, to

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correlate that response with outcome, and to determine whether preoperative chemotherapy resulted in increased rates of breast-conserving surgery and decreased rates of ipsilateral breast tumor recurrence. A total of 1,523 patients were enrolled; with a mean of 9.5 years of follow-up, no statistically significant differences were seen in survival between the groups (P=.80; relative risk [RR], 1.02; 95% CI, 0.84–1.21).[3,4] The 9-year survival was 70% in the postoperative group and 69% in the preoperative group. Based on the results of this study, the use of neoadjuvant chemotherapy is considered equivalent to adjuvant chemotherapy as far as long-term efficacy is concerned.

Can Response to Preoperative Therapy Predict for Long-Term Outcomes?

After 9 years of follow-up in the NSABP B18 clinical trial, the OS rate for patients experiencing pCR was 85%, compared with 73% for patients with pathologic nonresponse (pINV; invasive cells are present).[4] After adjustment for the other prognostic variables, patients with pCR had a 50% reduction in the risk of death compared with the group as a whole (RR, 0.50; 95% CI, 0.32–0.78); those with pINV had an 8% increase (RR, 1.08; 95% CI, 0.81–1.42); those with clinical partial response (cPR) had a 28% increase (RR, 1.28; 95% CI, 1.01–1.62); and those with clinical no response (cNR) had a 45% increase (RR, 1.45; 95% CI, 1.11–1.90).[4]

Subsequent to the NSABP B18 trial, other studies confirmed the importance of reaching pCR in the patient population with breast cancer as a whole.[4] The NSABP B-27 trial[4] randomized patients to preoperative AC followed by preoperative or postoperative docetaxel (100 mg/m^2 every 21 days) or no further treatment. Although after 8 years of follow-up OS was similar in the different treatment arms, pCR remained a highly significant predictor of improved DFS (hazard ratio [HR], 0.49; P<.0001) and OS (HR, 0.36; P<.0001).[4]

However, when results were analyzed based on breast cancer subtype, pCR did not seem to correlate with long-term outcomes in patients with hormone receptor–positive disease. More specifically, in an analysis of 6,377 patients receiving neoadjuvant anthracycline taxane–based chemotherapy from 7 randomized clinical trials, the German Study Group found that low proliferating luminal A–like tumors (defined as grade 1–2 tumors that were hormone receptor–positive and HER2-negative) showed no prognostic impact of pCR, whereas highly aggressive HER2-positive (nonluminal) and triple-negative tumors showed a significant prognostic impact of pCR. A heterogeneous pattern was seen for luminal B–like tumors (defined as grade 3 tumors that were hormone receptor–positive). Although pCR seemed to be prognostic in luminal B/HER2-negative tumors, it did not correlate with prognosis in luminal B/HER2-positive tumors.[5]

Cortazar et al[6] performed a meta-analysis on results from 11,995 patients from 12 neoadjuvant clinical trials. The results confirmed that on a patient-level analysis, pCR is a strong predictor of outcome in patients with high-grade hormone receptor–positive breast cancers, triple-negative breast cancer (TNBC), and HER2-positive breast cancers. However, on a trial-level analysis, pCR improvement did not significantly correlate with outcomes. This suggests that when different treatment arms are compared, pCR is not a good surrogate end point for OS. Although this report had several limitations regarding the trial-level analysis, including the fact that only one clinical trial included the use of trastuzumab as an adjunct to chemotherapy in patients with HER2-positive breast cancer, this may highlight an inherent issue with using pCR in approving new drugs in the adjuvant setting.

William J. Gradishar, MD

Dr. William J. Gradishar is the Betsy Bramsen Professor of Breast Oncology in the Division of Hematology and Medical Oncology, Department of Medicine, at the Feinberg School Medicine at Northwestern University, and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. He serves as Director of the Maggie Daley Center for Women's Cancer Care. He has been Chair of the Annual Lynn Sage Breast Cancer Symposium since its inception 16 years ago. He served as Program Director of the Hematology Oncology Fellowship Training Program at Northwester for 20 years. His research focuses on the development of novel therapeutics for the treatment of breast cancer.

He is a member of the Breast Cancer Core Committee of ECOG, the Committee on Cancer of the American College of Surgeons, Chair of the NCCN Breast Cancer Guidelines Panel, and member of the NCCN Breast Cancer Risk Reduction Guidelines Panel. In addition, he serves as a consultant to the Oncology Drug Advisory Committee of the FDA. He has published in the area of breast cancer therapeutics, with a focus on new endocrine therapy, chemotherapy and biologic agents.

Dr. Gradishar received his medical degree form the University of Illinois Abraham School Of Medicine in Chicago. He completed a residency and chief residency in internal medicine at Michael Reese Hospital and Medical Center in Chicago and a clinical research fellowship in medical oncology at the University of Chicago.

Can We Generalize Results From Neoadjuvant Clinical Trials to Predict Treatment Superiority in the Adjuvant Setting?

To date, one example of an adjuvant clinical trial with the goal of corroborating results from the neoadjuvant setting has been reported. Several neoadjuvant clinical trials suggested that dual HER2 blockade in the form of trastuzumab and lapatinib significantly improves pCR. The NeoALTTO was an open-label, phase III trial in which 455 patients with HER2-positive, early-stage breast cancer (tumors >2 cm) were randomly assigned to lapatinib (1500 mg/d), trastuzumab (standard dose), or a combination of both agents (lapatinib, 1000 mg/d plus standard trastuzumab dosing).[7] The anti-HER2 therapy was administered alone for the first 6 weeks, at which point weekly paclitaxel was added to the assigned anti-HER2 therapy for an additional 12 weeks, followed by definitive surgery. After surgery, patients received adjuvant therapy along with the same anti-HER2 therapy as assigned preoperatively, for a total of 52 weeks of anti-HER2 therapy. The primary end point of the study was the pCR rate. The pCR rate was significantly higher in the group of patients receiving lapatinib and trastuzumab (51.3%) versus trastuzumab alone (29.5%) or lapatinib alone (24.7%). Additionally, the difference between trastuzumab alone and lapatinib alone was statistically significant in favor of trastuzumab.

The NSABP B-41 trial[8] accrued 529 women with early-stage breast cancer and found that dual HER2 blockade with trastuzumab and lapatinib produced higher pCR (62.0%) compared with trastuzumab (52.5%) and lapatinib (53.2%), although this did not reach statistical significance. Similarly, other clinical trials[9–11] showed a significant or nonsignificant improvement in pCR with the combination of trastuzumab and lapatinib compared with single-agent trastuzumab.

These results suggest that the ALTTO trial, the adjuvant version of the NeoALTTO trial, would show superior outcomes with the combination of trastuzumab and lapatinib.[12] On the ALTTO trial, a total of 8,381 patients with HER2-positive early-stage breast cancer received postoperative chemotherapy and were randomized into 4 treatment arms: (1) trastuzumab for a total of 1 year; (2) lapatinib for a total of 1 year; (3) trastuzumab and lapatinib for a total of 1 year; (4) trastuzumab for 3 months followed by lapatinib for 9 months. The trial's primary end point was DFS, with secondary end points including OS and toxicity. Although the trial surpassed its accrual goal of 8,000 patients, it fell short of the 850 DFS events needed, with a total of 555 DFS events occurring. During the first interim efficacy analysis, the lapatinib-only arm was discontinued and patients were crossed over to trastuzumab. With a median follow-up of 4.5 years, DFS was 86% in the trastuzumab arm, 87% in the trastuzumab followed by lapatinib arm, and 88% in the trastuzumab and lapatinib arm. No significant difference was noted between the trastuzumab versus trastuzumab/lapatinib arms (HR, 0.84; 95% CI, 0.70–1.02) and the trastuzumab versus trastuzumab followed by lapatinib arms (HR, 0.96; 95% CI, 0.80–1.15). Similarly, no significant difference in OS was found between arms. However, an optimal dose of lapatinib could be given to only 60% to 78% of patients, whereas at least 90% of patients received an optimal dose of trastuzumab. Interestingly, a recent update of the NeoALTTO study that included long-term outcomes[13] showed no significant differences in event-free survival or OS between treatment arms, confirming the ALTTO trial results.

The lack of concordance between pCR and long-term outcome benefits between the neoadjuvant and adjuvant trials combining trastuzumab and lapatinib has several potential explanations. What magnitude of improvement in pCR is needed to translate into a significant event-free survival or OS benefit remains unclear. Furthermore, with the improvement in outcomes in early-stage breast cancer, many adjuvant clinical trials are hindered by being underpowered to show a significant difference in outcome between treatment arms. Additionally, several targeted therapies have substantial toxicities that may limit long-term use. As an example, in the ALTTO trial, a substantial number of patients were not able to take optimal doses of lapatinib. This may be more apparent with long

treatment duration versus in the neoadjuvant setting in which a medication is given for just a few months. Another potential explanation is that the patient populations participating in neoadjuvant and adjuvant clinical trials may be different. Typically, patients participating in neoadjuvant clinical trials have more advanced disease compared with those participating in adjuvant clinical trials. This was apparent in the NeoALTTO trial, in which less than 3% of the patient population had tumors 2 cm or smaller, whereas 45% in the ALTTO trial had tumors that size.[7,12] Finally, several neoadjuvant clinical trials include adjuvant treatment. This may lead to misinterpretation of a potential pCR benefit.

The Approval of Pertuzumab

In 2014, the FDA granted accelerated approval for pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either >2 cm in diameter or node-positive) as part of a complete treatment regimen for early-stage breast cancer. This approval was based on results from 2 neoadjuvant clinical trials, the NeoSphere and the TRYPHAENA.[14,15] In the NeoSphere trial, a total of 417 patients with early-stage HER2-positive breast cancer were randomized to receive 4 cycles in one of 4 treatment arms: (1) docetaxel and trastuzumab; (2) docetaxel and pertuzumab; (3) pertuzumab and trastuzumab; (4) docetaxel, pertuzumab, and trastuzumab.[14] After surgery, patients received anthracycline-based chemotherapy and trastuzumab, whereas the dual antibody arm also received docetaxel postoperatively. The results showed that the combination arm with docetaxel, pertuzumab, and trastuzumab had a significantly improved pCR at 39.3% compared with 21.5% in the docetaxel and trastuzumab arm. In the TRYPHAENA trial, all patients received neoadjuvant chemotherapy with the combination of pertuzumab and trastuzumab for early-stage HER2-positive breast cancer.[15] All treatment arms produced high pCR rates, ranging from 54.7% to 63.6%.[15]

This accelerated approval is provisional, based on the results of the upcoming APHINITY trial (ClinicalTrials.gov identifier: NCT01358877), an adjuvant randomized clinical trial evaluating the efficacy of combination pertuzumab and trastuzumab compared with single-agent trastuzumab. Other data that led to the FDA granting accelerated approval for pertuzumab included the significant OS benefit in the metastatic setting and the fact that APHINITY had already completed accrual. The NCCN Breast Cancer Panel included pertuzumab in the NCCN Guidelines for treatment of early-stage breast cancer in the neoadjuvant/adjuvant setting. Furthermore, duration of therapy and whether therapy should be given strictly in the neoadjuvant or whether it could also be given in the adjuvant setting were left to the discretion of the treating physician pending results from the APHINITY trial.

Where Do We Go From Here?

The FDA, responding to valid concerns from patients, advocates, and physicians, has allowed for accelerated drug approval based on results from neoadjuvant clinical trials. Full drug approval still depends on large randomized phase III clinical trials confirming a DFS or OS benefit. This allows for a faster drug approval process, which is important, especially in patient populations with a high risk of disease recurrence. Physicians and patients should understand that aside from a lack of long-term outcome data, this approach also lacks long-term safety data. In the case of pertuzumab, results of the AFFINITY trial will provide both long-term safety and efficacy data.

Recently, data from the CALGB 40603 trial were presented.[16] This study was a randomized neoadjuvant phase II clinical trial evaluating the role of bevacizumab and carboplatin in TNBC. The trial had a 2 x 2 factorial design. Patients received preoperative chemotherapy with paclitaxel, 80 mg/m^2 weekly for 12 weeks followed by AC for 4 cycles.

Patients were randomized to receive bevacizumab, 10 mg/kg every 2 weeks for 9 doses and/or carboplatin area under the curve 6 every 3 weeks for 4 doses with the initiation of paclitaxel. The primary end point was pCR, but the study was not powered to detect differences in relapse-free survival or OS. The trial accrued 433 patients, and although no difference in pCR was seen with use of bevacizumab, a significant improvement was seen in pCR with the use of carboplatin (41% no carboplatin vs 54% with carboplatin; OR, 1.71; *P*=.0029).

So, how do the results from CALGB 40603 and NeoSphere/TRYPHAENA differ? Why is pertuzumab considered standard therapy for early-stage HER2-positive breast cancer but carboplatin is not considered standard therapy in early-stage TNBC? A major difference between these 2 scenarios is the fact that pertuzumab has shown an impressive OS benefit in the first-line therapy of metastatic HER2-positive breast cancer, whereas no data are available to suggest an OS benefit with the use of carboplatin in triple-negative metastatic breast cancer.[17] Furthermore, the AFFINITY trial is underway and has completed accrual, whereas an adjuvant phase III clinical trial incorporating carboplatin in TNBC is planned but has not yet opened to accrual.

For the time being, caution should temper the enthusiasm of results from neoadjuvant clinical trials. Patients need to be counseled on the lack of long-term efficacy and safety data. An individual's risk of recurrence should be considered in selecting the appropriate treatment plan. The completion of randomized phase III clinical trials will help guide our decision-making process.

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