Relevance of Pathological Complete Response after Neoadjuvant Therapy for Breast Cancer

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ABSTRACT: Breast cancer is a heterogeneous disease, and the different biological subtypes have different prognostic impacts. Neoadjuvant trials have recently become popular as they offer several advantages compared to traditional adjuvant trials. Studies have shown that patients who achieve pathological complete response (pCR) after neoadjuvant treatment have a better long-term outcome. Consequently, increasing the rate of pCR became the end point of neoadjuvant trials with the expectation of translation into improved survival. However, the definition of pCR has lacked uniformity, and the prognostic impact of achievement of pCR on survival in different breast cancer subtypes is uncertain. In this review, we present the controversies associated with the use of pCR as an end point in neoadjuvant trials.

KEYWORDS: pathological complete response, neoadjuvant, breast cancer

Introduction

Despite the improvement in the treatment of early stage breast cancer with cytotoxic chemotherapy to eradicate occult metastatic disease, a subgroup of patients continues to be at high risk for recurrence and death. Regimens that are given in the adjuvant setting are commonly used in the neoadjuvant setting. This practice is based on the evidence that survival is similar whether chemotherapy is given before or after surgery.[1,2] Preoperative or neoadjuvant chemotherapy (NAT), previously reserved for locally advanced or inflammatory breast cancer, is now used more widely as it offers several advantages, such as: (1) it may convert a previously unresectable, locally advanced breast cancer to an operable tumor; (2) in presenting operable tumors, downstaging can allow increased rate of breast conservation surgery; (3) it provides prognostic information and allows change or discontinuation of treatment in case of unresponsive tumors; and (4) it represents an optimal research setting to study biomarkers and intermediate end points.

Studies have shown that patients who achieve pathological complete response (pCR) after NAT have a better long-term outcome.[2] Consequently, increasing the rate of pCR became the end point of neoadjuvant trials with the expectation of translation into improved survival. However, the definition of pCR lacks uniformity, and the prediction of outcome may vary according to different biological subtypes. In this review, we present different definitions of pCR and the controversies associated with its use as an end point in neoadjuvant trials.

Neoadjuvant Clinical Trials

In contrast to phase III adjuvant trials (slow, recruiting a large sample size, expensive, inefficient, but addressing definitive end points of relapse and survival), neoadjuvant trials use smaller sample sizes, are less expensive, and provide rapid assessment of short-term efficacy. Recognizing the approval of new drugs for high-risk populations as a priority, but understanding that the traditional process to get a promising treatment approved in the market, is expensive (over 2 billion dollars) and long (10–15 years). The US Food and Drug Administration (FDA) announced the consideration for accelerated drug approval in early breast cancer on the basis of neoadjuvant clinical trials, establishing that the product "has an effect on a surrogate endpoint that is likely to predict clinical benefit."[3]

pCR as a Surrogate End Point for Survival

Tumor response to NAT has been considered as a good surrogate end point for survival; the achievement of pCR is strongly associated with favorable long-term survival rates[2,4,5] and is therefore recommended by the FDA as a primary end point in neoadjuvant trials with the expectation of translation into improved survival. In line with this approach, in September 2013, the FDA granted accelerated approval to pertuzumab for NAT of women with early stage breast cancer expressing human epidermal growth factor receptor 2 (HER2). The approval was granted on the basis of pCR results from the NeoSphere and TRYPHAENA[6,7] trials. Despite its widespread use, there

is still no uniform definition of pCR. Three definitions were most commonly used by different investigators:

- ypT0 ypN0: absence of invasive cancer and in situ cancer in the breast and axillary nodes
- ypT0/is ypN0: absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma in situ
- ypT0/is: absence of invasive cancer in the breast, irrespective of ductal carcinoma in situ or nodal involvement.

To investigate the potential of pCR as a surrogate end point for long-term outcomes, the FDA established a working group known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTneoBC). The CTneoBC analyzed about 13,000 patients enrolled in 12 large neoadjuvant clinical trials with available data for pCR, event-free survival (EFS), overall survival (OS), and a median follow-up of at least three years.[8] In the *responder analysis*, patients who achieved a pCR had a significant reduction in the risk of recurrence and death. The eradication of tumor from both breast and lymph nodes (ypT0/is ypN0 and ypT0 ypN0) compared to the absence of tumor in breast only (ypT0/is) has a stronger association with improved EFS and OS.

Based on these data, the FDA recognizes either of the following definitions of pCR for the purpose of designing trials for US marketing approval:

1. pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following the completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system) or
2. pCR is defined as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following the completion of neoadjuvant systemic therapy (ie, ypT0 ypN0 in the current American Joint Committee on Cancer [AJCC] staging system).

The major benefit in the long-term outcome from achieving a pCR was found in patients with aggressive breast cancer subtypes (triple-negative; HER2-positive and hormone-receptor-negative and high-grade hormone-receptor-positive, HER2-negative). These findings are in line with the evidence that pCR varies among breast cancer molecular subtypes. In particular, indolent ER-positive tumors (luminal A) are less responsive to chemotherapy, compared to the high-risk scores of subtypes,[9] and achievement of pCR predicts the improvement of only disease free survival (DFS) in triple-negative/basal-like, HER2-positive (nonluminal), or luminal B (HER2-negative) tumors.[10] Six molecular subtypes of triple-negative breast cancers (TNBCs) have been identified, with basal-like being the only one wherein significant

association exists between genomic signature, pCR, and survival after chemotherapy,[11] highlighting how tailoring therapy would require further stratification by the biological subtype.

However, the *trial–level analysis* in the CTneoBC report found no correlation between the magnitude of difference in pCR rates between treatment arms in each study and EFS or OS. It is possible that different biological subtypes of breast cancer require a different end point definition regarding pCR to indicate a survival benefit. The inclusion of heterogeneous populations may have obscured the association. Moreover, the absolute difference in pCR achieved between treatment arms was generally very small (1–11%), but as high as 20% for the NOAH trial (the only trial in which a certain correlation was found between the effect of pCR and long-term outcome).[8] Based on these data, the FDA suggested a set of criteria necessary for neoadjuvant trials to support accelerated approval.

One of the suggested criteria is that the trials should be randomized, controlled, and designed to demonstrate superiority of the new drug, which should be tested as an add-on design (comparing the investigational agent plus standard adjuvant regimen to standard regimen alone). In addition, the neoadjuvant trials should be integrated with a confirmatory adjuvant trial that is able to show significant survival benefit. Caution should be taken when there are discordant conclusions between neoadjuvant and adjuvant trials (eg, doubling in pCR observed with lapatinib plus trastuzumab in NeoALTTO[12] did not translate into improved survival outcome in the phase III adjuvant ALTTO trial presented at the 2014 American Society of Clinical Oncology.)[13] Similarly, whether the pCR results obtained with pertuzumab in NeoSphere[6] and TRYPHAENA trials[7] translate into improved survival will not be known until results from the ongoing APHINITY trial become available. Therefore, the FDA concluded that accelerated approval of a new drug can be made based on the significant improvement of pCR, but it should be reserved only for high-risk populations where the benefit outweighs the risk of marketing a drug without the support of long-term safety and survival advantage. However, the magnitude of *significant improvement* was not defined. Neoadjuvant studies on high-risk populations are expected to provide the strongest evidence of correlation between pCR and clinical outcome. Typically, this high-risk population is comprised of those with triple-negative, hormone-receptor (HR)-negative, HER2-positive breast cancers, and probably high-grade HR-positive breast cancers. These subpopulations experience an unfavorable prognosis with existing therapy compared to low-grade, HR-positive tumors that have a more favorable long-term prognosis and are more likely to be cured with currently available therapy. Such FDA guidance considers pCR a poor predictor of clinical benefit in this latter population. The reason why pCR does not correlate with survival in HR-positive breast cancer is not clear. In addition to their low sensitivity to chemotherapy and the indolent course of these cancers, early

dissemination of tumor cells and development of clonal evolution in distant sites were invoked.

As an additional point of controversy on the role of pCR achieved after NAT, there is no evidence of benefit from response-adjusted sequential therapy (the use of one chemotherapy regimen for a set number of cycles followed by clinical assessment of response, with subsequent administration of either the same or a noncross-resistant chemotherapy regimen in patients who failed to achieve pCR after the first regimen) based on a few clinical trials, such as the German GeparTrio[14] and the German Breast Cancer Study Group.[15] These two trials failed to demonstrate increased pCR and improved outcome in patients in the investigational arm who were switched to a different chemotherapy.

Future Directions in Neoadjuvant Trials

As previously discussed, neoadjuvant trials represent an optimal research setting. For example, these trials can help to individualize therapy with the identification of tumoral or circulating markers predictive of response to identify pathways to overcome therapeutic resistance. A new trial modality, the so-called *postneoadjuvant trial*, may be used to assess the efficacy of a new therapy compared to standard treatment for patients with residual disease after neoadjuvant therapy (eg, KATHERINE trial to evaluate the efficacy of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive breast cancer with residual tumor). Challenges in the neoadjuvant setting include an inaccurate assessment of early response to therapy and the lack of noninvasive means of predicting pCR to therapy in order to identify the best candidates for randomization early in the treatment course.

Breast imaging has failed to reliably assess pathological response to NAT: the correlation between tumor measurements by physical examination, imaging (mammography, ultrasound, or magnetic resonance imaging [MRI]), and tumor size on final pathology analysis is modest,[16–20] but concordance between tumor size on MRI and surgical pathology findings is higher for tumors with a well-defined MRI phenotype, especially TNBC and HER2-positive. In addition, Fludeoxyglucose F18 (18FDG) positron emission tomography (PET) has been shown to have good sensitivity (0.847; 95% CI: 0.793–0.892) but low specificity (0.661; 95% CI: 0.598–0.720).[21] As of now, there is no recognized method that could accurately predict pCR. On the other hand, the molecular basis for the pCR response rate among luminal subtypes is thought to reflect the inherent resistance to chemotherapeutics brought about by Bcl-2 expression patterns. Comparisons between luminal-type A and luminal-type B groups indicate that the proportion of the Bcl-2 high expression rate (>33%; $P = 0.013$) and the small size tumor (≤2 cm; $P = 0.001$) increased significantly in the luminal-type A group.[22] As a result, Bcl-2 might be considered as a potent prognostic factor in luminal-type breast cancer.[22]

For tumors expressing estrogen/progesterone receptor (ER/PR-positive), the neoadjuvant field has moved more generally toward strategies to omit chemotherapy in patients unlikely to derive benefit. Examples of this exploratory field are the development of the preoperative endocrine prognostic index score that integrates standard pathological staging parameters after neoadjuvant endocrine therapy with the measurement of ER status and level of Ki-67 proliferation antigen in the surgical specimen to predict recurrence rate[23] and the UK national trial POETIC (PreOperative Endocrine Therapy: Individualizing Care) that aims to validate whether changes in Ki-67 or in gene expression after two weeks of treatment with aromatase inhibitor may predict long-term outcome and may help to select patients who may need further adjuvant chemotherapy.

Approximately 75% of breast cancers are ER-positive, and most breast cancer deaths occur in ER-positive patients. ER-positive cancer is emerging as a significant continuing challenge to balance outcomes with treatment options. Late recurrences and an elevated risk of death beyond seven years are the characteristics of ER-positive cancer, which argue for additional treatment strategies for this population. The value of chemotherapy for patients with large luminal A breast tumors is unclear. Chemotherapy in the luminal A group may, in fact, increase relapse-free survival. It has been reported that survival declines during the first three to four years of follow-up for HER2-enriched and luminal B subtypes, followed by a slow decline in the subsequent years of follow-up. Basal-like subtype shows a similar rate of decline as the HER2-positive subtypes during the first 2–2.5 years, followed by a steady decline to about 13 years of follow-up. Interestingly, the curve for luminal A continued to decline steadily after 10 years of follow-up, suggesting that the risk of late mortality persists in this group. Luminal A subtype is the only subtype that continued a steady decline in survival during the 20-year period with little leveling off in the later years, according to the study results.[24] Consequently, patients with luminal A breast cancer could benefit from extended treatment, ultimately improving their chances of long-term survival. If we were to find a way to increase pCR in this group, will pCR for this subpopulation become predictive? In effect, if we could find a way to increase pCR in the luminal A group, we would change the paradigm of treatment for this group.

Conclusions

pCR varies significantly among different breast cancer subtypes and can be considered as an established prognostic factor in aggressive subtypes, such as triple-negative and HER2-positive breast cancer. The eradication of tumor from both breast and lymph nodes has a stronger association with improved EFS and OS. The use of pCR as a surrogate end point for survival remains unclear. Neoadjuvant clinical trials to support accelerated approval of investigational agents based on increased pCR should enroll uniform biological

subtypes with a high-risk disease. They should be designed as randomized, controlled trials that aim to demonstrate superiority of the new drug by an add-on design and be followed by additional trials to confirm significant survival benefit. Finally, improvement in pCR in the neoadjuvant setting can be used to screen drugs to move forward in the research process or for early approval but should not be considered predictive of survival benefit in the adjuvant setting unless it was followed by confirmatory adjuvant studies.

Author Contributions

Wrote the first draft of the manuscript: AP. Contributed to the writing of the manuscript: AP, TK, IM, LH. Jointly developed the structure and arguments for the paper: AP, TK, IM, LH. Made critical revisions and approved final version: AP, TK, IM, LH. All authors reviewed and approved of the final manuscript.

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