A Proposal to Redefine Pathologic Complete Remission as Endpoint following Neoadjuvant Chemotherapy in Early Breast Cancer

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Keywords

Breast cancer · Neoadjuvant chemotherapy · Pathologic complete remission

Abstract

Many analyses of the efficacy of neoadjuvant treatment (NAT) for early breast cancer including a meta-analysis derived from 10 randomized trials came to the conclusion that patients who would achieve pathologic complete response (pCR) following NAT would experience significant improvement in disease-free and overall survival (OS). Thus, pCR was proposed as a surrogate endpoint for OS, with pCR representing a robust prognostic marker for survival at an individual level. In the current analysis, we argue that OS following NAT-induced pCR might have reflected the initial prognosis of patients mainly defined – among other factors – by the initial pathological lymph node status while being largely independent on the type of administrated treatment, thus pleading against the pCR surrogacy hypothesis. We therefore propose to redefine pCR as a surrogate endpoint of NAT trials by the involvement of additional biologic parameters.

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Introduction

Results of clinical trials evaluating the efficacy of neoadjuvant treatment (NAT) in early breast cancer came to the unanimous conclusion that patients whose cancers would achieve pathologic complete response (pCR) (de-

fined as pT0/Tis, pN0) would experience a significant improvement in disease-free (DFS) and overall survival (OS), as compared to patients with residual disease [1–12].

Prevention of breast cancer relapses has also been extensively documented to be achieved upon the use of adjuvant treatments, although the results of randomized trials need several years or even decades to become mature [13]. In contrast, NAT and its surrogate parameter of pathologic tumor remission is usually available within a few months after having started treatment. As NAT looks similarly effective as adjuvant treatment in preventing relapses [14], pCR was proposed as a surrogate endpoint for OS, thus defining superiority of a specific regimen over the other within a relatively short time frame [15]. As a consequence, the regulatory agencies FDA and EMA have announced that they would embark upon accelerated approval processes by the use of pCR as a surrogate endpoint for the efficacy of drugs tested in the context of NATs [16, 17]. This decision was based on the results of a large, FDA-supported meta-analysis, which included 11,955 individual patient data from 10 randomized NAT trials [18] and validated pCR as a robust prognostic marker for survival at an individual level, meaning that patients who would have achieved pCR would have a longer DFS (HR = 0.48; 95% CI 0.43–0.54) and OS (HR = 0.36; 95% CI 0.31–0.42) than patients with residual disease. The data were more consistent for the triple-negative (TNBC) (HR = 0.25) and HER-2/neu overexpressing subtypes (HR = 0.39) of breast cancer.

Is pCR following NAT Prognostic or Predictive?

However, the meta-analysis could not validate the causal relationship between the magnitude of pCR and survival improvement. The parameter used to assess this relationship was the coefficient of determination (R^2), which provides a quantitative estimate of how well changes in the presumptive surrogate endpoint (i.e., pCR) predict changes in the final endpoint (i.e., OS) [19]. In this model, R^2 of 0 indicates no association, R^2 of 1 a perfect association, whereas R^2 of 0.75 is considered an acceptable level to determine surrogacy [20, 21]. In the mentioned meta-analysis, the values for R^2 calculated to support the surrogacy of pCR for DFS ($R^2 = 0.03$) and OS ($R^2 = 0.24$) were far below the recommended 0.75 threshold, thus indicating no correlation at the trial level [18]. The same inconsistency was also evident in a meta-regression including 14,641 women from 29 NAT trials in which an only minimal association between the effect of treatment on pCR and the corresponding event-free survival ($R^2 = 0.08$) or OS ($R^2 = 0.09$) were reported [22].

It is, therefore, permissible to conclude that if two regimens are compared in a NAT randomized trial, the one inducing a higher pCR rate does not improve patient survival. More intriguingly, both analyses showed a positive slope of regression lines consistent with an inverse correlation between pCR increase and OS hazard ratio. A critical and provocative appraisal of these results might lead to the conclusion that treatments with a larger effect on pCR might have statistically correlated with worse survival.

Overlooking these discrepancies, the FDA has – for instance – granted an accelerated approval for the use of pertuzumab in the neoadjuvant setting for HER-2/neu overexpressing breast cancer, which was based on a significant improvement in pCR shown to have occurred in the NeoSphere Phase II trial [23, 24]. Following the FDA guidelines [16], 45% of the currently ongoing randomized NAT trials chose pCR as a primary endpoint for efficacy [25]. Recently, the results of some of these trials further promoted the surrogacy of pCR upon NAT [26–28].

Despite the mentioned important considerations regarding the efficacy of treatment modalities for early breast cancer, we believe that using pCR as a surrogate endpoint for OS in NAT trials refers to the prognostic rather predictive relevance of pCR, with the latter being only marginal.

Prognostic Significance of pCR following NAT

Patients included in the mentioned meta-analysis initially formed a mixed population in which the node-negative (N0) and node-positive (N⁺) individuals were pooled. Following NAT, N0 patients were translated into

the pN0 cohort, while N⁺ patients were moved into the pN⁺ cohort. There is no doubt that some N⁺ patients should have been converted into the pN0 subcategory due to NAT. An intuitive consideration would assume that N⁺ patients with a low nodal tumor load (i.e., 1–3 involved lymph nodes) could have been included into the pCR group, while the opposite might have occurred for patients with a high nodal tumor load (≥ 4), namely that they could have been included more likely into the non-pCR group.

It is worth noticing that the initial pathologic lymph node status was not known at the start of NAT (i.e., patients were stratified according to clinical lymph node status, [18]). Based upon a negative result in a multivariate analysis, the impact of this important prognostic factor upon outcome was neglected.

Similarly, patients with small primary tumors (T1–2) would have preferentially enriched the pCR cohort, whereas patients with larger tumors (T3–4) would preferentially enrich the non-pCR cohort. This trend is objectively illustrated in the meta-analysis, with 18–19% T1–2 tumors having been included in the pCR cohort, as compared to only 13–14% T3–T4 cancers [18]. Therefore, following NAT, the pCR cohort is likely to mainly contain patients and cancers with initially good prognosis (N0 or low lymph node burden, low T), whereas the non-pCR group would be likely to include the population with an initially poor prognosis (N⁺ or high nodal burden, high T). It might therefore be permitted to speculate that an identical OS outcome would have occurred with and without NAT.

This kind of interference of biological variables with outcome has been recognized in trials on the efficacy of adjuvant treatments by stratifying patients according to all known prognostic factors encountered after appropriate surgical staging. In addition, some other intrinsic tumor-related biomarkers (e.g., the presence of tumor-infiltrating lymphocytes or BRCA mutations in patients with TNBC) have been recently documented to correlate the pCR rate with OS regardless of the allocated NAT [29–33].

In summary, it is permissible to conclude that pCR following NAT reflected mainly the initial prognosis of patients and was largely independent on the type of administered treatment. However, it is not the aim of the current considerations to argue against the fact that pCR following NAT is correlated with OS *at the individual level*.

The Biologic Relevance of pCR upon NAT

There is no doubt that the pCR process extends beyond this course of enforcing the patients' initial prognosis. This extension is responsible for the difference in the pCR rate between various trial arms. However, the available data point to the fact that this process might most

likely reflect a biologic event without any impact on patients' outcome.

Summing up the above-mentioned considerations, we recommend discriminating between two pCR types: the *prognosis*- and the *biology*-related categories. Whereas *prognosis*-related pCRs occur independent of the type of NAT, their magnitude is limited to the proportion of patients with good prognosis in the pooled population, and is responsible for improved DFS and OS documented at the individual level. In contrast, the *biology*-related pCR denotes a pathologic process only, is variable in magnitude, depends on the administered NAT, but has no impact on survival.

Looking at the data from this perspective, the paradox of pCR can easily be solved: At the individual level, the survival improvement of patients with pCR is driven by the initial *prognosis* and has found to be independent of the allocated treatment [18, 34–36].

At the trial level, the analysis was performed by evaluating the impact of a certain NAT to increase the pCR rate, which, however, represents a dynamic process. This is based on *biology*-related pCR that depends on the type of NAT but has no impact on survival and thus no predictive relevance. This variable biologic process is responsible for the lack of correlation between pCR and OS at the trial level.

Results of Randomized Trials in HER2-Positive and TNBC Subsets

The independent evaluation of the neoadjuvant/adjuvant tandem trials performed in the HER-2/neu overexpressing subtype supports the lack of pCR surrogacy for OS. For instance, the neoALTTO trial showed a significant 74% improvement of the pCR rate in the combined trastuzumab-lapatinib chemotherapy arm as compared with the trastuzumab chemotherapy arm (51.3 vs. 29.5%, $p = 0.0001$) [37]. However, in the adjuvant setting, the double blockade was not better than the standard trastuzumab chemotherapy arm. (DFS = 85 vs. 83%; $p = \text{ns}$; OS: 93 vs. 91%, HR = 0.86; $p = 0.152$) [38]. A similar message

emerged from the NeoSphere/Aphynity tandem trials: in NeoSphere, the addition of pertuzumab to the trastuzumab chemotherapy backbone was associated with a 58% pCR improvement over the standard trastuzumab chemotherapy arm (45.8 vs. 29%; $p = 0.0141$) [24]. However, a disappointing 0.9% difference in invasive DFS was recorded when the identical regimens were compared for their efficacy in the adjuvant setting (3-year iDFS: 94.1 vs. 93.2%, HR = 0.81; $p = 0.045$; ref. [39]).

The same inconsistent pCR surrogacy value emerged from randomized trials performed in the TNBC subtype: The CALGB 40603 study included 443 TNBC patients to receive NAT $\pm$ carboplatin. The addition of carboplatin significantly improved the pCR rate (54 vs. 41%; $p = 0.0029$) but had no effect on the 3-year DFS (76 vs. 71%; HR = 0.84; $p = 0.36$). A positive correlation on an individual level was also noted: patients achieving pCR derived a significant survival benefit regardless of the allocated treatment (the 3-year OS rate was 93 vs. 73%; $p < 0.0001$) [12, 36]. The GeparSixto trial included a subset of 291 patients with TNBC, randomized to receive a taxane/anthracycline (+ bevacizumab) NAT with or without carboplatin: the pCR rates improved from 37 to 53% by the addition of carboplatin ($p = 0.005$), and a positive correlation with DFS was initially reported (85.8% with carboplatin vs. 76.1% without; HR = 0.56; $p = 0.0350$) [40]. However, mature results showed no significant impact of the addition of carboplatin on OS (HR = 0.60; $p = 0.10$) [41].

Conclusions

We conclude that substantial evidence pleads against the pCR surrogacy hypothesis. Continuing to use this endpoint in NAT trials may select for inappropriate, possibly more toxic regimens while discarding potentially efficient therapies. The difference between the *prognosis*- versus *biology*-related pCR can be made responsible for the pCR paradox. Therefore, we propose to redefine pCR as a surrogate endpoint of NAT trials according to the mentioned criteria setting the outcomes apart.

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