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Original article

Clinical usefulness and relevance of intermediate endpoints for cytotoxic neoadjuvant therapy

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ABSTRACT

Intermediate endpoints are surrogate markers of treatment efficacy assessed earlier than the true outcome of interest. Tumor response after systemic neoadjuvant therapy is considered a suitable intermediate endpoint, especially for specific breast cancer subtypes. Response can be evaluated either after only 1 cycle of treatment by clinical evaluation or at the end of the planned neoadjuvant treatment by histomorphologic examination of all surgically removed tissues from the breast and regional nodes. Although several meta-analyses showed a lower risk of death among patients who attain a pathologic complete response (pCR) compared with patients with residual tumor in breast and/or lymph nodes after neoadjuvant therapy, a statistically significant linkage between increased pCR rate by a specific treatment and improvement of survival by the same treatment has not been demonstrated yet. Therefore, formal surrogacy of pCR is not established. Moreover, the better definition of pCR is still an open issue: a large pooled analysis demonstrated that patients who attained ypT0 ypN0 (no invasive or non-invasive residual cancer in breast and nodes) experienced longer DFS ($p < 0.001$) compared with patients who attained ypTis ypN0 (no invasive residual in breast and nodes irrespective of residual non-invasive disease). Nevertheless, the Food and Drug Administration (FDA) recently allowed using pCR as a surrogate endpoint for accelerated approval process. Several meta-analyses demonstrated the greatest prognostic value of pCR in more aggressive breast cancer subtypes (i.e. triple-negative, HER2-positive, or high grade breast cancer). Usefulness of an earlier intermediate endpoints was prospectively demonstrated in the GeparTrio trial in which patients showing an early response achieved 4-times more frequently a pCR than those without early response.

Introduction

Neoadjuvant therapy is a reasonable treatment option for early-stage breast cancer patients who are candidate to receive systemic treatment. Over the last decades, neoadjuvant strategy has been compared with standard adjuvant therapy with the dual aims of downstaging disease to make it more easily resectable and improving survival. Even if no impact on survival can be demonstrated [1], neoadjuvant strategy offers several advantages: 1) conversion of unresectable and/or locally advanced breast cancer to an operable tumor [2,3] and, in primarily operable cancers, downstaging results in a significant increase in breast conservation rates [4,5]; 2) assessment of early clinical and molecular response, in order to avoid unnecessary toxicity in patients who potentially will not derive any benefits from the treatment and to increase treatment outcome by switching to another strategy; 3) correlation between achieving clinical/pathological response and long-term outcomes [6].

Accordingly, early tumor response and pathological complete response (pCR) can be considered suitable intermediate endpoints for cytotoxic neoadjuvant therapy.

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Relevance of intermediate endpoints in clinical trials and drug approval

An endpoint is a clinical or a laboratory outcome measured in a subject after randomization that allows the investigator to assess the effect of an independent variable (i.e. a new drug) on a dependent variable (i.e. survival) [7]. When designing a clinical trial, selection of an appropriate primary endpoint is fundamental because it impacts on the number of patients needed for the trial and the time required to complete the study and obtain meaningful results.

Historically, new drugs for breast cancer have been approved on the basis of relevant improvement in overall survival (OS) and disease-free survival (DFS). However, choice of survival as a primary endpoint can greatly increase study size, duration, and costs. Considering that clinical success rate of oncology drug approval in solid tumor indications is lower than 10% [8], recent financial analyses showed that development cost has increased dramatically and the development approached used over the past decades is no more sustainable [9]. Thus, intermediate endpoints reasonably likely to predict clinical benefit have become increasingly accepted as primary endpoint in clinical trials [10]. According to its definition, an intermediate endpoint is a surrogate marker of treatment efficacy assessed earlier than the true outcome of interest and it is hypothesized to be in the middle of the causal sequence relating the independent variable to the dependent variable [7].

The earliest indicator of treatment efficacy is a drug-induced tumor size decrease [11]. The potential of tumor response to predict a reduction in undetectable micrometastatic burden may lead to personalized systemic treatment as well as rapid assessment of new drugs. However, pCR has been shown to correlate with patient outcome better than early tumor shrinkage. Thus, complete response rate evaluated in the surgical specimen after neoadjuvant therapy has been frequently used as an intermediate endpoint in neoadjuvant setting and the Food and Drug Administration (FDA) has allowed the use of pCR as a surrogate endpoint for accelerated approval process [12].

However, several unsolved issues have still to be clarified:

Definition of pCR

There is general agreement that the preferred definition of pCR is the absence of residual invasive cancer within both the breast and lymph nodes [13]. However, the prognostic impact related to residual non-invasive tumor after systemic preoperative treatment is not totally defined and the FDA currently accepts two definitions for pCR: 1) no invasive and non-invasive residual cancer in breast and lymph nodes (ypT0 ypN0) [13,14]; and 2) no invasive residual in breast and nodes irrespective of residual non-invasive disease (ypT0/is ypN0) [15–17].

Pooled analyses have been conducted from different study groups with the aim to outline the best definition of pCR in term of prognostic discrimination. A retrospective analysis of a database including 2302 breast cancer patients treated with neoadjuvant chemotherapy at the M.D. Anderson Cancer Center between 1980 and 2004 showed a similar 10-year DFS rates (81.3% versus 81.7%, respectively) and 10-year OS rates (91.8% versus 92.5%, respectively) between patient who achieved ypT0 ypN0 and ypT0/is ypN0. The Authors concluded that residual in situ disease in patients who experience complete eradication of the invasive cancer in the breast and lymph nodes did not adversely affect survival [16]. On the other hand, a pooled analysis of 6377 subjects conducted by the German study group demonstrated that patients who attained ypT0 ypN0 experienced better DFS (hazard ratio [HR] 1.74; 95% confidence interval [95%CI] 1.28–2.36; $p < 0.001$) and a trend in better OS (HR 1.41; 95%CI 0.87–2.29; $p = 0.166$) compared with patients who attained ypT0/is ypN0. According to this larger analysis, the best prognostic discrimination is obtained including both no invasive and no non-invasive residual tumor in breast and lymph nodes in the pCR definition (ypT0 ypN0) [13].

Surrogacy of pCR for long-term survival outcomes

The relationship observed between response to neoadjuvant therapy and prognosis of patients with breast cancer does not automatically mean that treatment response is also a surrogate endpoint for long-term survival.

A recent meta-regression on 29 trials, for a total of more than 14,000 patients, did not support the use of pCR (whatever the definition) as a surrogate endpoint for DFS and OS in unselected patients with breast cancer (DFS $R^2 = 0.08$; 95% CI 0–0.47; and OS $R^2 = 0.09$; 95% CI 0.01–0.41) [18]. Accordingly, the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis on nearly 12,000 patients, enrolled in 12 international neoadjuvant randomized controlled trials, demonstrated a weak association between pCR (ypT0/is ypN0) and both event-free survival (EFS) and OS [19].

A potential explanation for the inability to demonstrate a clear correlation could be that the vast majority of the trials in both the pooled analyses enrolled women with heterogeneous breast cancer subtypes who underwent to different treatments with in average only marginal improvements of pCR. In fact, in the meta-regression analysis a better associations were found in a subset of trials comparing intensified/dose-dense chemotherapy versus standard-dose regimens (DFS: $R^2 = 0.79$; 95% CI 0.26–0.95; $p = 0.003$; and OS: $R^2 = 0.57$; 95% CI 0.19–0.93; $p = 0.03$), suggesting that pCR may potentially meet the criteria of surrogacy with specific systemic therapies [18]. Moreover, in the Neoadjuvant Herceptin (NOAH) trial, an absolute improvement in pCR of 20% (ypT0/is ypN0) results in a 36% reduction in risk of death or recurrence among women diagnosed with locally advanced breast cancer and treated with chemotherapy plus trastuzumab [20]. These results suggest that a correlation between pCR and survival outcomes may be identified in future trials conducted in selected breast cancer subtypes treated with more homogeneous therapy.

The non-confirmatory data recently assessed between the pCR improvement achieved with the addition of lapatinib to neoadjuvant paclitaxel and trastuzumab in the NeoALTTO trial [21] and the disappointing long-term results of ALLTO has raised some doubts about the value of pCR in HER2 positive disease [22]. However, two other neoadjuvant studies did not show a higher pCR rate with the addition of lapatinib to chemotherapy and trastuzumab, whereas the inferior outcome of the lapatinib monotherapy arm in ALTTO was correctly predicted e.g. by the neoadjuvant GeparQuinto study. In addition, adherence to a 1 year adjuvant treatment with lapatinib was much more impaired by cumulative toxicities as compared to a 12–24 week treatment in the neoadjuvant setting.

Clinical relevance of pCR and early tumor response in different breast cancer subtypes

The idea that pCR may not have the same prognostic relevance in all the breast cancer subtypes emerged from several analysis [13,23]. Recently, the CTNeoBC analysis provided inconfutable data supporting this hypothesis. The association between pCR and outcomes has been demonstrated to be greatest in aggressive tumor subtypes. Triple-negative breast cancer (TNBC) patients who achieved pCR experienced a risk of death reduced by 84%, HER2-positive/hormone receptor (HR)-negative breast cancer treated