Neoadjuvant therapy for ER-positive breast cancers

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ER-positive, HER-2-negative operable breast cancer represents a heterogeneous group of tumors. Tumor subtypes associated with different responses to neoadjuvant therapies can be identified through the evaluation of pathological features that include grade, the degree of expression of estrogen (ER) and progesterone (PgR) receptors and markers of cell proliferation such as Ki67 labeling index. For patients with a high proliferative index and/or a high grade who have a higher likelihood for a pathologic complete response, the selection of neoadjuvant chemotherapy should follow the same algorithm utilized for postoperative adjuvant treatments. In particular, both anthracyclines and taxanes should be evaluated for the chemotherapy regimen. Neoadjuvant endocrine therapy should be considered in place of cytotoxic neoadjuvant therapy for postmenopausal patients with tumors with low grade or proliferation and high ER and PgR expression. If given, such treatment should be continued for a minimum of 4–8 months. Selected patients with special types of breast cancer (e.g., pure tubular, cribriform and mucinous tumors) have a limited expected benefit from preoperative therapy and might receive adjuvant endocrine therapy alone. Tailored neoadjuvant treatments should be considered in patients with ER-positive tumors. Issues focusing on safety, quality of life and patient preference should be routinely discussed.

Key words: breast cancer, luminal subtype, neoadjuvant

Introduction

For patients with breast cancer, neoadjuvant therapy might be beneficial in several ways beyond the possibility of achieving a breast conservation surgery (BCS) in some of them. The response to the neoadjuvant treatment may be utilized as a prognostic marker, since it has been shown to be associated with a longer disease-free survival (DFS) compared with no response. In particular, it has been assumed that pathological complete remission (pCR) is a valid surrogate of long-term survival and cure from breast cancer [1–3]. Consequently, the information on the outcome associated with pCR to neoadjuvant therapy may allow switching from an ineffective regimen to a more effective intervention.

However, pCR can be achieved only in a minority of patients with ER-positive disease. Literature data indicate that pCR rates range from 2% to 10% in those patients whose tumors express estrogen receptors (ERs), suggesting that other primary end points must be considered within this subset of tumors [4, 5].

Conflicting results are reported in the literature on the value of factors predictive of response in the neoadjuvant setting, in particular in the subset of patients with ER-positive tumors. Biomarkers that might have a predictive value in patients treated with preoperative therapy include the degree of ER expression [6–8] grade [9], histotype [4] and markers of proliferation such as Ki67 labeling index [10].

Results from two randomized trials on neoadjuvant endocrine therapy in postmenopausal patients with ER-positive disease support the hypothesis of a correlation between the probability of response and the degree of ER expression. In particular, higher ER levels significantly correlated with a higher probability of response in both studies [6, 7]. Moreover, a positive significant correlation between the ER level and the degree of Ki-67 suppression after 2 and 12 weeks of endocrine treatment was reported [10]. On the other hand, the level of expression of ER and progesterone (PgR) might be correlated with the probability of response to neoadjuvant chemotherapy. In a retrospective analysis focusing on 533 patients, no pCR was observed within the cohort of patients defined as highly endocrine-responsive (ER and PgR expressed in ≥50% of the cells), which compares with 3.3% of those with ER or PgR expressed in 0%–49% of the cells and 17.7% of those with hormonal receptor absent tumors ($P < 0.0001$) [8].

The presence of elevated Ki-67 before neoadjuvant therapy has been found to predict response to chemotherapy in locally advanced breast cancer. In retrospective studies conducted on a large number of patients, high baseline Ki-67 was found to be an independent factor predictive for pCR at multivariate analyses [9, 11]. An important correlation between the degree of expression of Ki-67 after preoperative chemotherapy and outcome was also reported. In particular, higher Ki-67 levels after preoperative chemotherapy substantially and independently correlate with poorer DFS [12, 13].

Recent results indicate that Ki-67 might represent a valid surrogate of outcome in patients with ER-positive breast cancer treated with neoadjuvant endocrine therapy. In fact, tumor
Ki-67 levels determined during neoadjuvant endocrine treatment were found to be a marker of treatment efficacy and to have a substantial prognostic value [10, 14].

Moreover, Ki-67 data have been integrated into a post-treatment model (PEPI score) that also includes pathological stage and ER levels. The model was found useful to identify subsets of patients for whom adjuvant treatment without chemotherapy could be considered after a neoadjuvant endocrine treatment. In particular, in the IMPACT trial no relapses were recorded in patients with small node-negative tumors with a PEPI score of 0 (residual tumor with a low Ki67 index and with maintained ER expression) [15].

Obviously, consistent measurements of individual clinicopathological components are a crucial requirement. Guidelines have been recently published for ER and PgR receptor determination [16] and for adequate evaluation of Ki-67 [17].

Genetic testing on breast tumors has already identified distinct tumors that are associated with different responses to neoadjuvant therapies [18]. Tests that contain signatures for proliferation, ER- and PgR-regulated genes, such as the 21 gene Recurrence Score™, may have additional predictive value. In particular, advantages include a possible more precise evaluation of selected features as measured by quantitative RT-PCR if compared with IHC and biochemical assay, and central laboratory testing.

In ER-positive disease, the PAM50 intrinsic subtype analysis provided useful information for the identification of patient populations to be candidate for neoadjuvant endocrine therapy, with the exclusion of non-luminal intrinsically endocrine therapy-resistant tumors [19]. The Genomic Grade Index (GGI) was found to have a predictive and prognostic role. High GGI was associated with increased sensitivity to neoadjuvant chemotherapy that included paclitaxel plus fluorouracil, Adriamycin and cyclophosphamide chemotherapy in both ER-negative and ER-positive patients, and was correlated with a worse survival in ER-positive patients [20].

Other authors developed predictive signatures for resistance and response to neoadjuvant chemotherapy stratified according to ER status. A genomic predictor anticipated resistance or sensitivity to neoadjuvant chemotherapy and was able to identify patients with high probability of survival following taxane and anthracycline chemotherapy [21].

However, gene expression profiling would not be possible in the next future for the majority of patients. Moreover, it still remains inadequate today in the identification of the population which can avoid neoadjuvant chemotherapy or are candidates for a very high probability of pCR after chemotherapy in the subset of ER-positive disease. Owing to the frequent unavailability of the gene array analysis, a pragmatic approximation to the definition of intrinsic subtypes using immunohistochemical evaluation was recently proposed [22]. This approach identified two luminal HER-2-negative subtypes (luminal A and luminal B HER-2-negative) through immunohistochemical definition of ER and PgR receptor, the detection of overexpression and/or amplification of the HER-2 oncogene, and Ki-67 expression.

Although the characteristics of luminal A disease (expression of ER, low proliferation and no amplification or overexpression of HER-2 oncogene) might adequately define the subtype of breast cancer for clinical purposes in the neoadjuvant setting, the luminal A subtype is not routinely used as an eligibility or stratification criterion for neoadjuvant therapy studies.

### Specific considerations for neoadjuvant endocrine treatment choice

**Neoadjuvant endocrine treatment in postmenopausal breast cancer patients**

Historically, neoadjuvant endocrine therapy was limited to patients who were not suitable for chemotherapy and surgery. Earlier phase II studies with tamoxifen that focused primarily on elderly and/or frail patients often unselected for hormone receptor status of the tumor showed a response rate ranging from 49% to 68% [23].

Aromatase inhibitors (AIs) block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma [24]. Third-generation AIs include the non-steroidal inhibitors, letrozole and anastrozole, and the steroidal inhibitor, exemestane. The results of large trials conducted in the metastatic [25] and adjuvant setting [26], indicating better outcomes among women given AIs than among those given tamoxifen, supported the investigation of these agents in the neoadjuvant setting in postmenopausal women with hormone receptor-positive tumors.

The PO24 trial was a randomized, double-blind, multicenter study that compared the efficacy of 4 months of letrozole or tamoxifen as neoadjuvant therapy for postmenopausal women with ER- and/or PgR-positive locally advanced breast cancer (clinical stage II or III). None of the patients were considered to be candidates for BCS at baseline and 14% of the patients were considered ineligible for resection. Letrozole increased the clinical response rate (55% versus 36%, P < 0.001) and the BCS rate (45% versus 35%, P = 0.022) when compared with tamoxifen [27]. The superiority of letrozole was correlated with a higher degree of treatment-induced reduction in the mean Ki-67 levels in the surgical specimens (87% in the letrozole arm versus 75% in the tamoxifen arm) [28].

In the IMPACT study, postmenopausal women with ER-positive, operable breast cancers were randomly assigned to neoadjuvant tamoxifen, anastrozole or a combination of tamoxifen and anastrozole for 3 months. The response rate was similar among treatments (37% versus 36% versus 39%), although patients receiving anastrozole were significantly more likely to undergo BCS (46% versus 22%) [7]. Also in the PROACT trial, anastrozole and tamoxifen yielded a similar response rate. However, in the subgroup of patients treated with anastrozole who did not receive concurrent chemotherapy, a trend to increased response rate was observed (36.2% versus 26.5%, P = 0.09) [29]. Improved BCS rates in patients receiving AIs were reported in a meta-analysis conducted on these three studies [30].

Exemestane was compared with tamoxifen in a randomized study including 151 postmenopausal women with ER- and/or PgR-positive breast cancer. Exemestane significantly increased the clinical response rate (76% versus 40%, P = 0.05) and the rate of BCS (36.8% versus 20%, P = 0.05) if compared with tamoxifen [31].
A confirmation of the use of AIs in the neoadjuvant setting in ER-positive disease derives from the ACOSOG Z1031 trial. In this trial, 374 postmenopausal women with clinical stage II or III ER-positive breast cancer were randomly assigned to receive anastrozole, exemestane or letrozole for 16–18 weeks before surgery. The results of the study indicated that marked improvements in surgical outcomes are achievable with endocrine therapy with clinical response rates that were not statistically different among the three groups [19].

The optimal duration of neoadjuvant endocrine therapy has yet to be fully elucidated. However, an increased response rate was reported with neoadjuvant letrozole when the duration of therapy was extended beyond 3 months [32]. According to these results, it was recently agreed that hormonal therapy should be continued for a minimum of 4–8 months [22].

**neoadjuvant endocrine therapy combined with biological agents in postmenopausal patients**

There is strong rationale for the study in the neoadjuvant setting of endocrine therapy and signal transduction inhibitor combinations. Cross-talk between ER and growth factor receptor signaling pathways has been suggested as one of the mechanisms of endocrine resistance [33]. Crowder et al. [34] demonstrated that the inhibition of both PI3K-dependent and estradiol-dependent cell survival mechanisms leads to synthetic lethality. A new approach to restore endocrine responsiveness in breast tumors might therefore be the combination of an AI with a signal transduction inhibitor as a PI3K/mTOR antagonist.

Baselga et al. [35] conducted a neoadjuvant study on 270 postmenopausal women with ER-positive breast cancer, who were randomly assigned to receive letrozole plus everolimus versus letrozole alone. The combination of everolimus/letrozole demonstrated superior anti-proliferative effects and improved clinical response rate if compared with letrozole alone (68.1% versus 59.1%, respectively). Although these results are interesting, further studies are needed in order to establish the value of this type of combination in the neoadjuvant setting.

**neoadjuvant endocrine treatment in premenopausal patients**

Limited data are available on neoadjuvant treatments administered in premenopausal patients. In a study focusing on 13 premenopausal women with endocrine responsive disease, neoadjuvant therapy with a gonadotropin-releasing hormone (GnRH) analogue induced a 54% rate of clinical response after 3 months of treatment [36]. Torrisi et al. [37] analyzed the efficacy of letrozole in combination with GnRH analogues. The median duration of therapy was 5.2 months for letrozole. Thirty-two patients were considered assessable for response. One patient (3%) obtained a complete clinical response, which was confirmed as a pCR at pathological examination. Fifteen patients (47%) obtained a partial response, giving an overall response rate of 50%.

The STAGE study randomly assigned 204 premenopausal women with ER-positive, HER-2-negative disease, neoadjuvant chemotherapy combined with endocrine therapy. Data from in vitro studies [41] as well as results from adjuvant trials [42] indicate that concurrent use of chemotherapy and tamoxifen should be avoided. It was subsequently agreed that, weeks before surgery. More patients in the anastrozole group had a complete or partial response than did those in the tamoxifen group during 24 weeks of neoadjuvant treatment (70.4% versus 50.5%, respectively) [38].

These studies suggest that neoadjuvant endocrine therapy with a combination of GnRH analogue and AIs is effective in selected premenopausal patients. However, owing to the limited results available, new studies are required to confirm the role of ovarian suppression plus AIs in premenopausal women. Currently, the combination of GnRH analogues and AIs should only be given in the context of a clinical trial.

**specific considerations for neoadjuvant chemotherapy choice**

The selection of neoadjuvant chemotherapy for patients with ER-positive should use the same algorithm utilized for postoperative adjuvant treatments. In particular, no single preferred chemotherapy for ER-positive disease can be identified and both anthracyclines and taxanes should be considered in the selection of the chemotherapy regimen (concurrently or sequentially for at least six cycles or 6 months, respectively) [4, 22]. Mature available studies were in fact designed in an era when neoadjuvant therapies were selected according to the stage of the disease and where ‘tailored’ therapies were uncommonly taken into consideration. Only recently, breast cancer was recognized as a heterogeneous disease in which the chance that one treatment program will benefit all is not realistic.

Data from randomized studies support a prolonged duration for chemotherapy, when indicated, in ER-positive disease. The NSABP-B 27 trial was designed to determine the effect on pCR of adding docetaxel after four courses of preoperative doxorubicin and cyclophoshamide. An increase in pCR rates with prolonged chemotherapy (four more courses of docetaxel) was observed both in ER-positive and ER-negative tumors [39].

More recently, von Minckwitz et al. [40] reported the results of pooled analysis of the German neoadjuvant chemotherapy trials including more than 3000 women. The aim of the study was to correlate the treatment response across different breast cancer subtypes with the cumulative dose of chemotherapy, the number of courses and the addition of drugs. The authors reported that the number of courses of chemotherapy was the most important treatment factor. Association of pCR with increase in number of courses appeared more pronounced in hormone receptor-positive tumors [odds ratio (OR) 1.35] than in hormone receptor-negative tumors (OR 1.04; P-value for interaction = 0.046). In particular, in patients with hormone receptor-positive, HER-2-negative disease, the association of pCR with increase in number of cycles was statistically significant with an OR of 1.3 (95% CI 1.02–1.65).
also in the neoadjuvant setting, endocrine therapy should be given sequentially after chemotherapy [43].

New endocrine treatment options, such as GnRH analogues, alone or in combination with AIs, in premenopausal women may not require similar sequential administration. In particular, the efficacy of letrozole or letrozole plus oral low-dose cyclophosphamide was explored in one trial that randomized 114 elderly patients with locally advanced ER-positive breast cancer. A higher response rate (89.2% versus 72.8%) was observed for the combination [44]. The activity and tolerability of neoadjuvant letrozole plus GnRH analogue in combination with chemotherapy were recently investigated in 119 premenopausal patients with large operable ER-positive disease. The concurrent administration of letrozole, GnRH analogue and chemotherapy was well tolerated and effective with a response rate and a pCR rate observed in 52% and 5% of the patients, respectively [45].

In conclusion, preliminary clinical data on the concurrent administration of AIs and chemotherapy are encouraging. However, the neoadjuvant chemoendocrine approach should still be considered as investigational and should not be used outside a clinical trial. Conversely, the concomitant use of any indicated chemotherapy with GnRH analogues might be considered as acceptable in women with a desire of pregnancy [43].

neoadjuvant chemotherapy combined with biological agents

New combinations of chemotherapy and targeted drugs are under evaluation in order to further increase the rate of pCR in patients with HER-2-negative subtypes. In the NSABP B-40 study, 1206 patients with HER-2-negative disease were randomly assigned to receive or not bevacizumab for the first six courses of neoadjuvant chemotherapy. Chemotherapy included docetaxel plus capcitabine, or docetaxel plus gemcitabine for four courses, followed by doxorubicin and cyclophosphamide for four courses. The addition of bevacizumab to neoadjuvant chemotherapy substantially increased the rate of pCR from 28.2% to 34.5%, with the effect of bevacizumab more pronounced in the ER-positive group (23% and 15% with or without bevacizumab, respectively) [46]. The reason why the greatest benefit was seen in patients with hormone receptor-positive tumors was undefined. Moreover, these results were in contrast to the findings in the GeparQuinto trial in which the benefit was mainly registered in patients with hormone receptor-negative tumors [47]. Considering the differences observed in the results of the two studies as well as the increased incidence of toxic effects with the addition of bevacizumab, new data are needed before changes in the clinical practice can be considered.

neoadjuvant treatment of luminal special types

Within luminal breast cancer, several special types display an extremely good prognosis often approaching or equaling that of the general population. In particular, pure tubular and cribriform carcinomas are rare histological carcinomas, correlated with a very favorable prognosis [48]. Mucinous carcinoma, if present in pure form, might also predict a high 10-year survival rate [49], although conflicting data are reported in the literature about the outcome of this special type [48]. These tumors, in particular, if of limited size and clinically node-negative, can be properly managed with adjuvant endocrine alone without a neoadjuvant approach.

Invasive lobular carcinoma (ILC) (classic, alveolar, solid, pleomorphic, tubulo-lobular) is the most common 'special type' breast cancer. ILC is characterized by a low, if any, pCR rate (0%–3%) and a greater need for mastectomy if compared with invasive ductal carcinoma [4, 43, 50]. These data support a tailored approach in large ILC (e.g. neoadjuvant endocrine therapy administered for a prolonged period of time in postmenopausal patients) based upon proper evaluation of the cost–benefit ratio.

conclusions

Appropriate neoadjuvant systemic therapy involves choosing treatments tailored to individual patients according to biological features, assessments of patient risk, comorbidities and preference. ER-positive, HER-2-negative operable breast cancer represents a mixed group of tumors where the identification of distinct clinical entities is the key achievement for proper management. On the one extreme, patients with ER-positive, HER-2-negative disease may have tumors with very low risks of recurrence, where there is little evidence supporting the use of neoadjuvant therapy. On the other extreme, patients may present with high-risk, highly proliferative disease, where prolonged neoadjuvant chemotherapy appears clearly justified. Therefore, patients and their physicians must weigh the risks and benefits of all therapeutic options. Definition of specific niches of patients for tailored neoadjuvant treatment investigation is key to make progress on how to treat individual patients with ER-positive breast cancer.

disclosure

The authors have declared no conflicts of interest.

references


