The recent progress of neoadjuvant chemotherapy in triple negative breast cancer: A short review

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Abstract

Triple negative breast cancer (TNBC) encompasses tumors that do not express either the estrogen receptor (ER) or the progesterone receptor (PR) and also do not overexpress the Human Epidermal growth factor Receptor 2 (HER2). This is a heterogenous group of tumors that significantly overlaps with both basal-like tumors and BRCA1/BRCA2 mutation-associated tumors. TNBC is highly aggressive in nature and exhibits worse prognosis than the other subtypes of breast cancer, despite its increased chemosensitivity. Neoadjuvant chemotherapy (NACT) is a treatment option regularly incorporated in clinical practice to improve subsequent surgical management. In parallel, allows rating of the pathological compete response (pCR) which is associated with the prognosis of these patients and evaluates the efficacy of the applied treatment as well. Platinum-based regimens and novel targeted therapies have shown some benefit in TNBC, though an unmet need for improved therapeutic strategies in this patient population still remains. In this review, the latest progresses in NACT in TNBC are discussed, along with the improved understanding of molecular targets and useful biomarkers in this group of patients.

Key words

Triple negative breast cancer, Neoadjuvant chemotherapy, Progesterone receptor

1 Introduction

Breast cancer is a heterogenous disease and clinical, histopathological and molecular characteristics have been used for its classification. These cases that by immunohistochemical means do not express either the estrogen receptor or the progesterone receptor and also do not overexpress the HER2 are designated as “Triple Negative” Breast Carcinomas (TNBC) [1]. TNBCs account for 15% of all breast carcinomas and are usually diagnosed in younger women with advanced stage disease [2, 3]. TNBCs also tend to recur earlier and show a more aggressive metastatic phenotype than other types of this disease [4]. The lack of Hormone Receptor (HR) expression as well as the absence of HER2 overexpression in this subset of tumors is translated into clinical practice as shortage of therapeutic options for TNBC, essentially rendering a
deeper understanding in the pathogenesis of TNBC. The heterogeneity of this subtype of breast carcinoma and the role of NACT in its management will be discussed in this review, encompassing major trials announced up to the end of 2014.

2 TNBC-subtypes

In 2000, Perou et al. [5] identified five distinct subtypes of breast cancer by analyzing gene profiling produced by cDNA microarrays from 40 breast cancer patients. Among them, “basal-like” tumors that expressed breast basal cell keratins and were negative for HR expression demonstrated similarities with TNBC. However, not all TNBC are “basal-like” and these two terms cannot be used interchangeably. Histologically, the majority of TNBCs are invasive ductal carcinomas not-otherwise specified (IDC-NOS), but also rare entities such as medullary and metaplastic carcinomas, as well as apocrine and adenoid cystic carcinomas share the triple negative phenotype [6, 7]. Analogously, the heterogeneity among TNBCs is confirmed by molecular analysis [8, 9]. Although basal-like phenotype predominates among TNBCs -characterized by BRCA1/2 deficiency [10, 11] and frequent p53 mutations [12] - other subtypes have also emerged recently. Among them the claudin-low phenotype is the most prevalent one [13, 14]. These tumors demonstrate decreased expression of claudin proteins, which are important components of tight junctions between epithelial cells, and express markers of Epithelial to Mesenchymal Transition (EMT) [15, 16]. A recent molecular profiling of TNBCs conducted by Lehmann et al. [17] identified 6 TNBC subtypes displaying unique gene expression and ontologies, including 2 basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal-androgen receptor (LAR) subtype, the latter including patients with decreased relapse-free survival and characterized by androgen receptor (AR) signaling. Despite TNBC as a whole is considered more chemosensitive than other subtypes of breast cancer, differences in the efficacy of chemotherapeutic regimens have been shown also among subtypes of TNBC providing evidence that this should not be considered as a unique entity and paving the way for new targeted therapies based on the molecular characteristics of each subtype.

3 The rationale of neoadjuvant chemotherapy (NACT)

Traditionally, neoadjuvant chemotherapy (NACT) is used in patients with unresectable locally advanced breast cancer in an attempt to render the disease operable. However, the use of neoadjuvant chemotherapy has been extended also in primary operable tumors, in order to allow greater conservation of the breast and avoid mastectomy. From a clinical point of view, this approach is acceptable as shown by a recent meta-analysis demonstrating no difference in overall survival (OS) of patients with breast cancer subjected to surgery, independently of the setting chemotherapy was administered (adjuvant or NACT) [18]. In addition, response to NACT may also allow the modification of adjuvant radiotherapy decreasing the long-term consequences of breast cancer survivors, but this remains to be elucidated. NACT also offers the clinician two significant information: response to treatment thus enabling the appropriate design of subsequent therapies and prognostic information for the patient. It is now acceptable that patients who achieve pathological complete response (pCR) after NACT appear to have significantly lower recurrence rate in comparison to those with residual disease upon surgery [19-21]. This is particularly true for patients with TNBC [20, 22] and those with HER2-positive tumors treated with trastuzumab [21]. The last finding provides one more use for NACT: that of allowing investigators to examine efficacy of new chemotherapeutic regimens, as well as the modulation of biomarkers from initial biopsy to definitive surgery in order to gain approval for new treatments. This is particularly useful for aggressive subtypes of breast cancer, such as TNBC, and this modality has been adopted from regulatory agencies for providing accelerated approval for new drugs since studies based on adjuvant chemotherapy take much more time to be completed [23].

4 Neoadjuvant chemotherapy in TNBC

NACT is an essential clinical approach in specific inoperable locally advanced breast carcinomas aiming at reducing tumor size and rendering the tumor operable. Historically, though, the first neoadjuvant trials aimed at investigating
whether presurgical chemotherapy could be an alternative to postsurgical treatment in terms of disease-free survival (DFS) and overall survival (OS) and mainly in which population this is possible. This was based on the assumption that presurgical systematic therapy would act on a less multiclonal population of malignant cells increasing its efficacy in comparison to the adjuvant chemotherapy. In 2001, Wolmark et al. presented the results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 protocol comparing four cycles of doxorubicin and cyclophosphamide applied either in the neoadjuvant or adjuvant setting [24] in patients with operable breast cancer. No statistical significant differences, regarding DFS and OS, were noted between the two groups, despite patients with better primary tumor response had a favorable outcome. This result was later confirmed by a meta-analysis of nine studies -including the NSABP B-18- comparing adjuvant chemotherapy to NACT [18].

The correlation between complete response of the primary tumor after NACT and improved DFS and OS was repeatedly shown by various studies [25-27]. Patients with TNBC have increased rates of pCR in comparison to other histological types of breast cancer and these patients have an excellent prognosis [28]. However, those that do not acquire pCR have a much poorer prognosis despite the type of chemotherapy they received, and account for the overall worse outcome of this histology that is usually referred as the “triple-negative paradox” [29]. These were clearly demonstrated by a meta-analysis performed by von Minckwitz et al., encompassing seven prior studies of NACT in breast cancer [30-37]. This study clearly indicated that pCR defined as absence of invasive cancer in the breast and axillary nodes, and absence of ductal carcinoma in situ (ypT0ypN0) is a suitable surrogate marker of good prognosis for luminal B, HER2-positive and TNBC patients prompting for efforts to maximize pCR rates after NACT in these groups. Classical anthracycline- and taxane-based chemotherapy regimens used in the studies that were included in the von Minckwitz meta-analysis led to pCR in 31% of TNBC patients.

Attempts to improve NACT efficacy included intensified schemes and incorporation of new drugs in the already existed regimens. Following the increased efficacy of dose-dense chemotherapeutic regimens in the adjuvant setting, the implementation of such schemes in the presurgical setting also provided increased pCR rates in TNBC patients. In the PREPARE study [35], dose-dense sequential chemotherapy with epirubicin and cyclophosphamide followed by paclitaxel and finally by CMF led to a pCR rate of 44.6% in the TNBC group in comparison to the 30.4% achieved with the conventional schemes. Analogous results were documented with the GEPARDUO study [30] where patients received four cycles of docetaxel and doxorubicin, every 2 weeks, with the support of filgrastim.

Another therapeutic option is the incorporation of new drugs into regimens already established. BRCA1 germline mutations carriers often present tumors with basal-like morphology and their genomic alterations, as examined by microarray-based comparative genomic hybridization (array CGH), are similar to those in TNBC patients [10]. Finally, BRCA1 promoter methylation is a frequent event in TNBC patients and it predicts sensitivity to adjuvant chemotherapy [38]. In cancer cell lines and xenografted tumors, BRCA1 CpG island promoter hypermethylation-associated silencing predicts enhanced sensitivity to platinum-derived drugs to the same extent as BRCA1 mutations. Most importantly, BRCA1 hypermethylation proves to be a predictor of longer time to relapse and improved OS in ovarian cancer patients undergoing chemotherapy with cisplatin [39]. Under this perspective single agent cisplatin NACT resulted in pCR in 21% of patients with TNBC [40], while carboplatin and taxane combinations resulted in even greater response rates [41, 42]. Despite taxane- and anthracycline-based regimens remain the mainstay for TNBC neoadjuvant treatment, these encouraging results indicate that carboplatin-taxane regimens could be a very efficacious non-anthracycline containing combination. An ongoing phase III trial of the Netherlands Cancer Institute, investigates whether intensifying alkylating agents NACT could improve response rates in comparison to standard anthracycline- and taxane-based preoperative chemotherapy [43]. Analogously, in the randomized phase II GEPARSIXTO trial the addition of carboplatin to the standard anthracycline-taxane neoadjuvant regimen increased pCR ratio to over 50% of patients with TNBC [44]. This increase was statistical significant but was also associated with an increase in grade 3 and 4 hematological adverse events and diarrhea. Also, the number of patients that discontinued treatment due to toxicity was significantly greater in the carboplatin arm.
An alternative approach has emerged by the substitution of paclitaxel by its nanoparticle albumin-bound formulation. Weekly Nab-paclitaxel has been shown increased efficacy versus 3-weekly docetaxel administration in patients with metastatic breast cancer \[45\]. Analogously, nab-paclitaxel was associated with increased pCR rates compared to paclitaxel in taxane-first sequential taxane/anthracycline neoadjuvant treatment (GeparSepto trial) \[46\]. This was particularly evident in the TNBC patients population, where nab-paclitaxel increased statistically significant pCR rate from 25.7% to 48.2% (\(P < .001\)). This is a very important finding, as we know that pCR is most prognostic for outcome in this specific high-risk subtype, which comprises about 15% of all breast cancers.

5 Novel agents in the neoadjuvant treatment of TNBC

The efficacy of taxane- and anthracycline-based regimens in inducing pCR after neoadjuvant administration has reached a plateau. This became particularly evident in the study of Bear \textit{et al.}\[44\] who randomly assigned patients with operable, HER2-negative breast cancer to receive neoadjuvant therapy consisting of docetaxel, docetaxel plus capecitabine, or docetaxel plus gemcitabine for four cycles, with all regimens followed by treatment with doxorubicin-cyclophosphamide for four cycles. The addition of capecitabine or gemcitabine to docetaxel therapy, as compared with docetaxel therapy alone, did not significantly increase the rate of pathological complete response. In the same study, patients were also randomized to receive or not bevacizumab for the first six cycles of chemotherapy. The addition of the monoclonal antibody to NACT significantly increased the rate of pathological complete response and this benefit tended to be seen in patients with a high tumor grade and positive hormone receptors. Improved understanding of the molecular pathways regulating TNBC pathogenesis allows now for the introduction of targeted therapies that could provide clinical benefit. Based on the rationale that proangiogenic pathways are not extensively deregulated in early breast cancer, the anti-VEGF antibody bevacizumab could prove more efficacious in the neoadjuvant setting in comparison to the results shown by its use in patients with metastatic disease \([47\_49]\). In the GEPARQUINTO trial \[50\], bevacizumab indeed improved pCR rate in the studied population. The effect though was most prominent in patients with TNBC where the pCR rate raised from 27% with the conventional regimen of epirubicin plus cyclophosphamide followed by docetaxel to 39% when bevacizumab was added. More recently, in a Korean phase II study (KCSG BR-0905)neoadjuvant therapy with bevacizumab, docetaxel and carboplatin resulted in a pCR rate of 42% in patients with TNBC \[51\]. This rate was similar to that observed in another phase II study that combined bevacizumab with docetaxel and cyclophosphamide for four cycles followed by four cycles of doxorubicin \[52\], as well as with the rate of pCR achieved among patients with TNBC in the GEPARQUINTO trial as previously described. Further validation of these results is anticipated in order to clarify what could be the role of bevacizumab in the neoadjuvant setting of TNBC and specifically to delineate the subgroup of women who could benefit most and furthermore which type of chemotherapy is most suitable. The CALGB 40603 study, a phase II 2X2 factorial trial, will examine both the benefit of adding carboplatin to the taxane-anthracycline backbone, as well as the effect of incorporating bevacizumab in the preoperative chemotherapy of operable TNBC.

One of the most frequently altered pathway in breast cancer and specifically in TNBC is PI3K/Akt/mTor pathway \[53\]. Currently, everolimus an mTor inhibitor has gain regulatory approval for use in women with Hormone Receptor positive metastatic breast cancer that progress after first line hormonal treatment \[54\]. However, this drug as well as many others under development that inhibit at different levels the PI3K/Akt/mTor pathway has also been studied in TNBC patients. Everolimus in the neoadjuvant setting was studied in an open label randomized phase II trial in combination with the Paclitaxel-FEC regimen \[55\]. The addition of everolimus increased both Response Rate and pCR but not to a statistical significant extent. Furthermore, response to everolimus was not related to the downregulation of mTor pathway as shown by biomarker analysis. It should be noted though that everolimus was administered weekly at 30 mg per os in this study instead of the approved daily scheduled of 10 mg. Everolimus addition to paclitaxel in the neoadjuvant setting also failed to increase pCR rates in TNBC patients that were non-responsive to epirubicin-cyclophosphamide ± bevacizumab in the GeparQuinto study \[56\]. Long-term outcomes of these studies are awaited, but they clearly signify these agents may be beneficial, but better biomarkers should be discovered to guide for optimal selections of patients.
In TNBC, higher EGFR expression and increased EGFR gene copy number has been associated with worse prognosis [57, 58]. Also the EGFR expression is higher in TNBC among breast cancer patients [59]. These data prompted two phase II randomized studies that tested the role of cetuximab in patients with metastatic TNBC. Cetuximab used as monotherapy provided poor response rates [60], despite the EGFR pathway is active in these patients indicating that alternative pathway activation mechanisms exist in these patients. The addition of cetuximab though to cisplatin improved responses in the metastatic setting in comparison to cisplatin monotherapy despite the study did not met predefined criteria for OS and PFS [61] indicating that EGFR inhibition could have therapeutic benefit in these patients. Another EGFR inhibitor, erlotinib, has also shown encouraging pCR rates when combined with Carboplatin-Docetaxel chemotherapy in a small phase II trial [62]. Under this perspective a trial testing erlotinib along with chemotherapy in the neoadjuvant setting in women with TNBC is underway (NCT00491816). Finally, cetuximab is currently tested in combination with ixabepilone that has shown efficacy in a previous neoadjuvant trial in TNBC patients [63] in the NCT01097642 clinical trial.

Another attractive target in TNBC is PARP inhibition. In BRCA1/2 mutated tumours further inhibition of PARP provokes cell death through “synthetic lethality” [64]. TNBC shares clinical and pathological features with hereditary BRCA1-related breast cancer and BRCA1 deficiency in these tumors is frequent through various mechanisms leading TNBC to acquire a “BRCAness” phenotype [10]. Furthermore, analysis of cPARP expression in breast cancer patients treated with neoadjuvant chemotherapy in the GEPARTRIO trial indicated that cPARP was a strong predictive marker for pCR in triple negative tumors, while the same time was prognostic for more aggressive tumors resulting in worst OS and DFS for patients that did not achieve pCR [65]. Despite these promising indications and the positive results from a randomized phase II trial [66], iniparib a third generation PARP inhibitor failed to improve the outcome in the metastatic setting when added to cytotoxic chemotherapy [67]. Analogously, the interim analysis of the SOLTINeoPARP trial, a randomized phase II study that examined the efficacy of iniparib addition to weekly paclitaxel in the neoadjuvant setting of TNBC, failed to meet its primary endpoint that was pCR improvement [68]. Newer in vitro data though recognized that iniparib is not a selective PARP inhibitor [69, 70] and its antineoplastic action could be attributed to the modification of cystein-containing proteins [69], explaining its failure in the TNBC population. Other selective third generation PARP inhibitors, namely olaparib and veliparib, could be more effective and are investigated in clinical trials.

Table 1. Clinical trials investigating the role of targeted therapies in the neoadjuvant treatment of triple negative breast cancer

<table>
<thead>
<tr>
<th>Trial Identifier No</th>
<th>Phase</th>
<th>Investigated regimen</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0087575</td>
<td>I/II</td>
<td>Paclitaxel/Carboplatin/Sunitinib</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT0167668</td>
<td>II</td>
<td>Paclitaxel and LCL-161/placebo</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT00491816</td>
<td>II</td>
<td>Neoadjuvant chemotherapy (physician discretion) and erlotinib</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT00776773</td>
<td>II</td>
<td>Nab-paclitaxel/carboplatin followed by Docetaxel/cyclophosphamide with bevacizumab</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT0197642</td>
<td>II</td>
<td>Cetuximab/ixabepilone</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT0060249</td>
<td>II</td>
<td>Cetuximab/Docetaxel</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT01238133</td>
<td>I</td>
<td>Gamma-secretase/Notch signalling pathway inhibitor RO4929097/Docetaxel/Carboplatin</td>
<td>MTD/DLT of RO4929097</td>
</tr>
<tr>
<td>NCT0194869</td>
<td>II</td>
<td>Sorafenib/Cisplatin followed by ddPaclitaxel</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT0118063</td>
<td>II</td>
<td>Paclitaxel/carboplatin/Veliparib or placebo followed by Doxorubicin/Cyclophosphamide</td>
<td>pCR</td>
</tr>
<tr>
<td>NCT00861705</td>
<td>II</td>
<td>Paclitaxel±Carboplatin±Bevacizumab followed by Doxorubicin/Cyclophosphamide</td>
<td>pCR</td>
</tr>
</tbody>
</table>

6 Future perspectives

TNBC is a heterogenous disease that lack standard therapeutic approaches either in the early or advanced disease. Novel molecular techniques have though provided helpful insight in the molecular pathogenesis of this entity allowing for improved understanding of the several subtypes of TNBC [8, 12, 15]. These could be particularly useful in the neoadjuvant setting, that apart of providing optimal clinical benefit in patients with primarily inoperable as well as operable breast
cancer, allow also for gathering valuable information for recognizing biomarkers and novel therapeutic strategies. Novel targeted therapies have lately incorporated in regimens used in the preoperative setting in TNBC and many more are under investigation (see Table 1). The results of these trials will prove how beneficiary this targeted strategy could be for the patients, targeting a new era with less chemotherapy but more efficient regimens.

References


