Neoadjuvant treatments for triple-negative breast cancer (TNBC)

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Neoadjuvant chemotherapy provides a means both of improving subsequent surgical intervention and of testing novel therapies or combinations. Historically, triple-negative breast cancer (TNBC) has responded well in the neoadjuvant setting, with rates of pathological complete response (pCR) commonly higher than for other breast tumour types. However, more than half of TNBC patients do not achieve a pCR and have a very poor prognosis. The lack of drug-targetable receptors on TNBC tumours has made improving the available interventions in TNBC an area of important medical need. The routine use of neoadjuvant anthracycline/taxane combinations in TNBC is currently being supplemented by ongoing investigations of their use with other types of agent. In particular, the substantial proportion of TNBC tumours associated with BRCA1 mutations is driving clinical research into the use of DNA-damaging agents such as platinums, as well as of potentiators of DNA damage such as the investigational agent iniparib and inhibitors of poly-ADP ribose polymerase such as olaparib. Tyrosine kinase receptor inhibitors and microtubule-targeting inhibitors of cell cycling are also under active investigation. The use of neoadjuvant treatment with pCR as a surrogate of overall survival will allow the rapid evaluation and comparison of these and other much-needed new treatments for TNBC. Key words: chemotherapy, neoadjuvant, triple-negative breast cancer

introduction

Neoadjuvant treatment describes therapeutic intervention prior to surgery. In breast cancer, the aim of neoadjuvant treatment has historically been to reduce the size of unresectable tumours, allowing surgery to be performed. In addition, for operable tumours, neoadjuvant treatment allows for greater conservation of the breast and a decreased need for mastectomy. Today, neoadjuvant therapy is also increasingly viewed as a platform for testing novel therapies. Patients are treated de novo, with the analysis of tissues possible both before and after therapy. As response in some breast cancer subtypes to neoadjuvant treatment is linked with the long-term outcome, this enables rapid conclusions from studies involving a relatively small number of patients.

triple-negative breast cancer (TNBC) subtype responds well to cytotoxic chemotherapy

Triple-negative breast cancer (TNBC) tumours lack expression of oestrogen receptors (ER) and progesterone receptors (PR) and do not overexpress human epidermal growth factor receptor-2 (HER2) [1]. Retrospective analyses of large clinical trials concluded that the lack of ER expression in breast tumours predicts for a greater response to cytotoxic chemotherapy than tumours that are ER positive [2, 3]. These studies analysed over 6000 women with ER-poor breast cancer enrolled in 46 polychemotherapy trials. Compared with women not receiving chemotherapy, ER-poor patients showed a substantial reduction in the risk of recurrence, breast cancer mortality and death from any cause. One of these studies demonstrated that the 10-year recurrence rate in women aged <50 years receiving polychemotherapy was 33% compared with 45% for those in the same age group not receiving polychemotherapy (event ratio = 0.73, P < 0.00001); and for women aged 50–69 years, the 10-year recurrence rate rose to 42% for those receiving chemotherapy compared with 52% for those not (event ratio = 0.82, P < 0.00001) [2].

Experimenting with dose-dense or metronomic chemotherapy regimens has revealed differential results in patients with breast cancer depending on receptor expression [4]. A retrospective study (WSG AM-01) evaluated a dose-dense regimen of four cycles of epirubicin and cyclophosphamide followed by three cycles of cyclophosphamide, methotrexate, fluorouracil (CMF) compared with high-dose chemotherapy and peripheral stem cell support in high-risk patients with breast cancer [5]. Among patients with TNBC, overall survival (OS) was 76% for those receiving high-dose chemotherapy compared with 61% in the dose-dense arm [hazard ratio (HR)=0.58, 95% confidence interval (CI) 0.39–0.87, P = 0.007]. von Minckwitz et al. [6] investigated whether dosing characteristics of neoadjuvant therapy are associated with pathological complete response (pCR). Analysis of pooled data from 3332 women revealed a correlation between pCR and an increase in the
number of cycles of treatment given. Although hormone receptor-positive patients benefitted from a longer treatment duration [odds ratio (OR)=1.35, pCR increase for every two further cycles], patients with triple-negative tumours did not show such a correlation (OR = 1.09) [6]. Taken together, these studies support the benefits of dose-dense or dose-intensive chemotherapy regimens for TNBC [7–10].

neoadjuvant therapy benefits TNBC over non-TNBC tumours

Evidence from accumulated neoadjuvant studies revealed that pCR provides a surrogate marker that is predictive for long-term clinical response and survival in TNBC patients [11]. However, this was only found to be true when pCR was defined as no residual disease present in both the breast and axilla. First-generation neoadjuvant studies compared the same regimen in the pre- and post-surgical settings, and largely demonstrated no difference or a worse response with neoadjuvant chemotherapy [12]. Later studies compared different neoadjuvant treatments and tried to link improvements in pCR rates with improvements in disease-free survival (DFS) [13]. In a large study (N = 1118), Liedtke et al. [13] found that pCR rates were higher with neoadjuvant treatment in patients with TNBC compared with those with non-TNBC (22% versus 11%; P = 0.034) [13]. More recently, von Minckwitz et al. [14] presented the largest meta-analysis study to date comprising data from 6377 patients with operable or locally advanced, non-metastatic breast cancer having received neoadjuvant anthracyclines, taxanes with or without trastuzumab [14]. This study aimed to validate various definitions of pCR, and to determine the prognostic impact of pCR on DFS and OS in various breast cancer subgroups. The authors concluded that pCR should be conservatively defined as ypT0 ypN0 excluding ductal carcinoma in situ, and that pCR is an effective surrogate for survival for luminal B (HER2-negative), HER2-positive (non-luminal) and TNBC tumours, but not for luminal A or luminal B/HER2-positive tumours. Huober et al. [15] noted that the response to neoadjuvant treatment by TNBC tumours can be very rapid, with a response seen after only two cycles of therapy [15]. This highlights the need for early monitoring of patients with appropriate upfront localisation of the tumour (via a clip or tattoo) to aid with tumour localisation when surgery takes place after neoadjuvant treatment.

current neoadjuvant treatments and regimens

 Anthracycline/taxane chemotherapy-based regimens have routinely been used in the neoadjuvant setting for TNBC [16]. Huober et al. [15] reported a pCR rate of 39% in 509 patients with TNBC treated with TAC (docetaxel/doxorubicin/cyclophosphamide) or TAC-NX (docetaxel/doxorubicin/cyclophosphamide-vinorelbine/capecitabine), which represents the highest pCR rate reported to date in a large-scale multicentre trial. In agreement, a study by Di Leo et al. [17], measuring DFS in 294 patients with TNBC, also suggested a beneficial effect of anthracyclines compared with CMF therapy. However, recent studies challenge the role of anthracyclines in early-stage TNBC [18].

In a small (N = 204) hypothesis-generating study, patients with TNBC/basal-like breast cancer demonstrated a poorer response to anthracycline-based therapy compared with other breast cancer subtypes [19, 20]. Conversely, in the same study, patients with TNBC/basal-like breast cancer responded better to taxane-based therapy over other subtypes [20]. Avoiding unnecessary anthracycline treatment would be desirable given its associated cardiotoxicity [21]. In current practice, both drugs are still given in combination. The dosing characteristics of such combinations were investigated by von Minckwitz et al. [6] with the results supporting a concept of tailoring neoadjuvant chemotherapy regimens according breast cancer tumour type to maximise the efficacy of the therapy combination. The study concluded that for patients with TNBC in particular, treatment with higher cumulative doses of anthracyclines (≥300 mg/m 2 doxorubicin or equivalent) and taxanes (≥400 mg/m 2 docetaxel or equivalent) showed higher pCR rates (OR = 1.49 and 1.73, respectively) when compared with treatment results with lower cumulative doses [6].

The use of platinum agents has received renewed interest in the treatment of TNBC. There are histopathological similarities between BRCA1-mutated breast cancer tumours and TNBC, and TNBC is strongly associated with germline mutations in the BRCA1 gene (90% of BRCA1-mutated tumours are TNBC [22, 23]). Cells with BRCA1 mutations are deficient in DNA repair mechanisms, which make them sensitive to platinum agents [24]. For example, in one study, 6 (21%) of 28 patients with TNBC achieved pCR with single-agent neoadjuvant cisplatin (four cycles of cisplatin at 75 mg/m 2 every 21 days) [25]. However, improved responses have been shown when platinum-containing therapies are combined with taxanes in patients with TNBC compared with non-TNBC. Although small (between 9 and 24 patients), mostly single-site and single-arm studies have indicated platinum/taxane combinations provide good response rates in TNBC (Table 1), this potential benefit might be restricted to patients who are positive for BRCA1 mutations [26, 27].

The GeparSixto study, which started recruitment in 2011, will explore the additional use of neoadjuvant weekly carboplatin with an anthracycline-taxane-based combination treatment in 600 patients with TNBC or HER2-positive operable breast cancer [28]. The study aims to determine whether the addition of carboplatin increases the pCR rate of taxane regimens in TNBC disease (Table 2). The CALGB 40603 asks a comparable question but uses an anthracycline-free chemotherapy backbone (clinicaltrials.gov Nr. NCT00861705).

using the neoadjuvant setting to assess treatment options for TNBC

Neoadjuvant treatment can be used as a research tool to assess the efficacy of new drugs and/or new schedules with a validated surrogate end point [29, 30]. It also represents a model to evaluate relationships between treatments and tumour biomarkers [31, 32]. Clinical trials of novel, targeted neoadjuvant treatments in TNBC are ongoing (Table 2).
**vascular endothelial growth factor (VEGF) inhibitors**

VEGF inhibitors block the growth of tumour neovasculature. Recent studies assessing therapy combinations including the VEGF inhibitor bevacizumab have shown conflicting results. Gerber et al. [33] showed that the addition of bevacizumab to neoadjuvant chemotherapy significantly increased the pCR rate specifically in the TNBC patient subgroup (28% versus 36%, P = 0.021). Bear et al. [34] reported that the addition of bevacizumab to docetaxel/anthracycline-based regimens increased clinical and pCR rates; but, in contrast to von Minckwitz et al. [35], most of the effect was seen in the HR-positive patient subset (11.5% versus 17%, P = 0.033 compared with 41% versus 44%, P = 0.458 in patients with TNBC). The neoadjuvant CALGB 40603 study again randomizes patients with TNBC to bevacizumab or not and will report data in 2013 (clinical.trials.gov No. NCT00861705). However, it should be noted that the FDA approval of bevacizumab in breast cancer, including TNBC, has been withdrawn, although it is still available in Europe. This was based on the bulk of the evidence showing that current data do not support efficacy, and demonstrate increased toxicity [36]. Other antiangiogenic agents, including the anti-VEGF receptor tyrosine kinase inhibitors, sunitinib and sorafenib, are currently being investigated in the neoadjuvant setting; sunitinib with paclitaxel/carboplatin (NCT00887575) [37] and sorafenib in combination with cisplatin followed by paclitaxel for early-stage TNBC (NCT01194869) [37].

**epothilones**

Ongoing trials of new treatments include the microtubule-targeting agents, epothilones, a class of drugs in which the mode of action interferes with tubulin and prevents cell division [38]. In early trials, epithilones demonstrated improved efficacy and milder adverse effects than taxanes [38]. The epithilone, ixabepilone, has shown improved pCR rates in ER/PR-negative tumours compared with tumours positive for hormone receptors in a neoadjuvant trial [39]. Ixabepilone is currently being evaluated in a neoadjuvant trial in TNBC, in combination with the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab (NCT01097642) [37].

**EGFR inhibitors**

EGFR is overexpressed in TNBC, and although it has not yet been reported to be predictive of response to EGFR inhibition in other tumour types, it is a negative prognostic factor in TNBC [40]. A neoadjuvant trial investigating erlotinib (which specifically inhibits the EGFR tyrosine kinase) together with chemotherapy is currently ongoing (NCT00491816) [37].

**poly-ADP ribose polymerase (PARP) inhibitors**

Inhibitors of the enzyme PARP are being investigated as a possible treatment of TNBC. In tumours with BRCA1 or BRCA2 mutations, inhibition of PARP1 further compromises DNA repair leading to cell death. This makes the inhibition of PARP an attractive target for TNBC tumours that are BRCA1.

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**Table 1. Pathological complete response rates with current neoadjuvant treatments and regimens in triple-negative breast cancer**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>TNBC (N)</th>
<th>pCR (%)</th>
<th>pCR definition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline/taxane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC/FAC/AC</td>
<td>14</td>
<td>20% (P = 0.0001)</td>
<td>pCR in breast and axilla</td>
<td>Liedtke et al. [13]</td>
</tr>
<tr>
<td>TFEC/TFAC</td>
<td>35</td>
<td>28% (P = 0.0071)</td>
<td>pCR in breast and axilla</td>
<td>von Minckwitz et al. [6]</td>
</tr>
<tr>
<td>Anthracyclines/taxanesa</td>
<td>542</td>
<td>34% (TNBC &lt; 0.001)</td>
<td>pCR in breast and axilla</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24% non-TNBC (P &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum alone</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cisplatinb</td>
<td>28</td>
<td>21%</td>
<td>pCR in breast</td>
<td>Silver et al. [25]</td>
</tr>
<tr>
<td>Platinum/taxane</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Paclitaxel/carboplatinb</td>
<td>12</td>
<td>67% versus 12% (ER+/HR−) (P = 0.002)</td>
<td>pCR in breast and axilla</td>
<td>Sikov et al. [9]</td>
</tr>
<tr>
<td>Docetaxel/carboplatinb</td>
<td>24</td>
<td>33%</td>
<td>pCR in breast plus axilla</td>
<td>Chen et al. [45]</td>
</tr>
<tr>
<td>Docetaxel/carboplatinb</td>
<td>13</td>
<td>77%</td>
<td>pCR in breast</td>
<td>Kern et al. [46]</td>
</tr>
<tr>
<td>Docetaxel/carboplatinb</td>
<td>9</td>
<td>44%</td>
<td>pCR in breast and axilla</td>
<td>Roy et al. [47]</td>
</tr>
<tr>
<td>Docetaxel/carboplatinb</td>
<td>11</td>
<td>55%</td>
<td>pCR in breast</td>
<td>Chang et al. [48]</td>
</tr>
</tbody>
</table>

TNBC, triple-negative breast cancer; pCR, pathological complete response; FEC, fluorouracil, epirubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; AC, doxorubicin, cyclophosphamide; TFEC, weekly/once every 3 weeks paclitaxel/docetaxel followed by fluorouracil, epirubicin, cyclophosphamide; TFAC, weekly/once every 3 weeks paclitaxel/docetaxel followed by fluorouracil, doxorubicin, cyclophosphamide; ER, oestrogen receptor; HR, hormone receptor; AUC, area under curve.

*Multivariable analysis of treatment characteristics.

†Four treatments of cisplatin at 75 mg/m^2^ every 21 days were administered, 95% CI 9% to 43%.

‡Carboplatin AUC 6 q4w and paclitaxel 80 mg/m^2^ weekly for 16 weeks.

§Single-arm study: weekly paclitaxel 80 mg/m^2^ plus carboplatin AUC 2 weekly.

∥Ongoing trials of new treatments include the microtubule-targeting agents, epothilones, a class of drugs in which the...
deficient, and a clinical trial with olaparib is ongoing in TNBC [41]. The use of the PARP inhibitor olaparib in the treatment of TNBC patients without BRCA mutations has recently been shown to be ineffective [42]. The SOLTI NeoPARP study failed to show improved pCR rates by adding iniparib (which is not considered an inhibitor of PARP any longer) to neoadjuvant weekly paclitaxel [43]. However, expression studies of cytoplasmic PARP detected by immunohistochemistry in 640 patients treated in the neoadjuvant GeparTrio study revealed that PARP was not restricted to TNBC with BRCA1 or BRCA2 mutations, but was also detected in other breast cancer subtypes, especially HER2 positive. There was a strong positive correlation of cytoplasmic PARP expression with pCR but a negative correlation with survival [44].

conclusion

The neoadjuvant setting together with a pCR correlating to a favourable outcome in TNBC is a useful tool to enable rapid and effective evaluation of much needed new targets and treatments for TNBC. Despite a better response to neoadjuvant treatments over non-TNBC tumours, the long-term prognosis of TNBC patients overall is poorer than that of other breast cancer subtypes, particularly in the first 3 years after treatment. Patients achieving pCR have an at least similar survival compared with non-TNBC patients, but survival for TNBC patients with residual disease remains poor in comparison. This paradox may be explained by the presence of residual, resistant disease remaining in the majority of patients (>60%) [14]. The lack of cell-surface markers in TNBC renders these tumours insensitive to conventional treatments targeting the hormone receptors or HER2. New treatment approaches are currently being evaluated in clinical trials, which target tumour angiogenesis and genetic instability. Neoadjuvant therapy together with pCR as a surrogate marker for improved OS provides a means for testing much needed novel treatment options for TNBC patients. A potential trial design could start with chemotherapy first and randomise only those patients after surgery that did not achieve a pCR.

acknowledgements

Editorial assistance was provided by ArticulateScience Ltd., funded by Sanofi. The authors retain full control of content.

disclosure

GvM has received research grants from Sanofi and has been compensated as member of a Speakers Bureau for Sanofi. MM has nothing to disclose.

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