Preoperative therapy: what, when and for whom?

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**preoperative therapy: for whom?**

Preoperative systemic therapy (PST) is widely accepted as one of the standard treatments for patients with operable early breast cancer, as well as those with locally advanced disease for whom surgery alone will have limited benefits [2]. The latter case usually applies to patients with stage IIIA/IIIB or T3/T4 tumors, those with classic inflammatory breast cancer and those with involvement of ipsilateral supra- or infraclavicular lymph nodes (N3).

The International Expert Panel on the use of PST of operable breast cancer recommended this approach as a valid treatment option for the following patients [2]:

- those with operable breast cancer who are appropriate candidates for mastectomy but who desire less extensive surgery;
- those who can undergo a lumpectomy but whose physical appearance may be less damaged if PST is given first;
- those who wish to take advantage of a response assessment of their tumor before it is removed. A demonstrable response to PST may have a positive effect on the patient’s compliance with further therapy;
- those who may have medical contraindications to surgery or who wish to delay surgery. For example, PST can be given in the second or third trimester of pregnancy, followed by surgery and radiotherapy after parturition.

Preoperative endocrine therapy may be effective but its use as PST alone is appropriate mainly for frail postmenopausal patients or elderly patients in whom surgery would carry increased risk due to the patient’s advanced age or comorbidities. Even if pathological complete remission (pCR) rates are very low (~1%), mastectomy could be avoided in up to 40% of patients after endocrine therapy if they are carefully selected e.g. by high content of hormonal receptors [3].

**preoperative therapy: when?**

for patients with the need to improve their surgical options

Significant improvements in breast conservation have been observed with the use of neo-adjuvant chemotherapy (Table 1) [4]. For example, in the NSABP-B27 study, 62% of patients who received preoperative chemotherapy with doxorubicin–cyclophosphamide (AC) (n = 1533) and 64% of those who received PST with AC–paclitaxel (T) (n = 722) had successful breast conserving surgery (BCS) [5]. Among patients who had a clinical complete response (cCR) to PST, 70% underwent lumpectomies, compared with 56% of those without a cCR (P < 0.001). For patients with a pathological complete response (pCR), 71% underwent BCS compared with 60% of those with invasive cancer in the breast (P < 0.001). In the GeparTrio pilot study [6], including 16% of patients with T4 tumors, BCS was possible in 72% of patients overall. Among patients who showed a response to initial TAC chemotherapy 86% underwent BCS, compared with 66% of patients who showed no response.

Not all patients who receive PST are candidates for BCS. To aid patient selection for BCS after PST, a series of selection criteria have been developed [a score of 1 and low score (0–1) is good with few breast or loco-regional recurrences, high score (3–4) poor with >40% breast or loco-regional recurrences] [7], and a prognostic index for in-breast and loco-regional recurrence [8]. The latter comprises clinical N2 and N3 status, residual pathological tumor size >2 cm, lympho-vascular invasion and a multifocal pattern of residual disease. So far, however, no long-term follow-up with regard to surgical outcome is available from these studies, so that it remains unclear whether this initial benefit of higher BCS can be maintained.

**for patients where information on response and biology of disease is requested**

Assessment of efficacy in the adjuvant setting requires long-term follow-up. If the same treatment is given preoperatively an interim response can be determined at surgery or even during neo-adjuvant treatment. pCR in removed breast and axillary tissue is considered indicative of complete eradication of loco-regional disease, and has been proposed as a surrogate marker of the eradication of distant micrometastatic residual disease and of survival. Evidence supporting this view is provided by
the higher survival rates consistently observed in patients with a pCR following PST [9, 10]. In the large NSABP-27 trial, analysis of the 7-year follow-up data showed that pCR was a highly significant predictor of improved disease-free survival (DFS) [hazard ratio (HR) 0.45, $P < 0.0001$] and OS [HR 0.33, 95% confidence interval (CI) 0.23, 0.47; $P < 0.0001$] [11].

Whereas at surgery pathologic response evaluation represents the gold standard, a general method of evaluation during treatment is not recommended. Sonography allows serial examinations; however, reproducibility might not be satisfactory and not all tumors can be measured. Mammography has sufficient reproducibility, but serial examinations are restricted and again, not all tumors can be evaluated. Larger series using magnetic resonance imaging (MRI) are still not evaluable, but show a substantial number of false positive residuals before surgery. Positron-emission tomography (PET) within 1–3 weeks after first chemotherapy application was investigated for its potential role as an early predictor of response; however, larger series are not available in the literature.

In the GeparTrio trial, the response to the first two cycles of preoperative TAC chemotherapy was investigated as a method for identifying patients who might subsequently achieve high or, conversely, minimal pCR rates [12]. Patients with untreated breast cancer initially received two cycles of TAC as PST and were assessed for response. Then, patients with a clinical response were randomized to receive either four ($n = 704$) or six ($n = 686$) further cycles of TAC. Patients with no response to the initial treatment were randomized to receive either four more cycles of TAC ($n = 321$) or NX (vinorelbine, capecitabine; $n = 301$). Approximately one quarter of responders achieved a pCR after six or eight cycles of TAC chemotherapy, with no statistically significant difference between these two treatment groups. In contrast, the pCR rate was only 5–6% amongst non-responders, including those switched to NX therapy. Multivariate analysis of the GeparTrio results (Table 2) identified estrogen receptor (ER) status as having a predictive value for achieving a pCR, with ER-negative patients having a greater chance of a pCR than ER-positive patients. These data indicate that initial response to PST does have predictive value for overall response to therapy.

## Table 1. Breast conservation rates after neo-adjuvant therapy [4]

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Treatment</th>
<th>Breast conservation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-18 [16]</td>
<td>1523</td>
<td>AC</td>
<td>60</td>
</tr>
<tr>
<td>ECTO [17]</td>
<td>1355</td>
<td>AP-CMF</td>
<td>67</td>
</tr>
<tr>
<td>EORTC [18]</td>
<td>448</td>
<td>FEC</td>
<td>34</td>
</tr>
<tr>
<td>Scholl [9]</td>
<td>414</td>
<td>FAC</td>
<td>65</td>
</tr>
<tr>
<td>NSABP B-27 [19]</td>
<td>2411</td>
<td>AC/AC-D</td>
<td>–</td>
</tr>
<tr>
<td>Geparduo [21]</td>
<td>913</td>
<td>ADdd/AC-D</td>
<td>61</td>
</tr>
<tr>
<td>Gepartrio (pilot) [22]</td>
<td>286</td>
<td>DAC/DAC-NX</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 2. Significant predictive factors for pathological complete remission in the GeparTrio study (multivariate analysis) [12]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All patients ($n = 1210$)</th>
<th>Responders ($n = 831$)</th>
<th>Non-responders ($n = 370$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>2.0</td>
<td>–</td>
<td>6.3</td>
<td>–</td>
</tr>
<tr>
<td>Tumour grade (3 versus 1 + 2)</td>
<td>2.7</td>
<td>2.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tumor type (ductal versus other)</td>
<td>2.2</td>
<td>2.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ER/ProgR (negative versus positive)</td>
<td>3.7</td>
<td>4.3</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>Complete response after 2 cycles</td>
<td>10.4</td>
<td>2.3</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Odds ratio against PST group with lowest pathological complete remission rate.

Abbreviations: ER, oestrogen receptor; NA, not applicable; ProgR, progesterone receptor.

## Preoperative therapy: what kind?

Several trials were conducted to compare adjuvant systemic treatment with the same treatment given preoperatively. In the majority of these trials similar survival rates have been shown for cyclophosphamide–methotrexate–5-fluorouracil (CMF), 5-fluorouracil–epirubicin–cyclophosphamide (FEC) and AC [1, 2].

In a second generation of trials, various preoperative therapies have been compared with each other, using pathologic response evaluation at surgery as an endpoint. In general, these newer trials all included docetaxel or paclitaxel as one component of PST. To allow a more focused view, only trials including >500 patients are discussed in the following section.

The NSABP B-27 trial [5, 11] evaluated the effect of adding either preoperative or postoperative docetaxel to preoperative AC chemotherapy in 2411 women with operable primary breast cancer. Results showed that neo-adjuvant chemotherapy with...
Table 3. Neo-adjuvant treatment regimens for breast cancer recommended by German Arbeitsgemeinschaft Gynäkologische Onkologie [21]

<table>
<thead>
<tr>
<th>Oxford Centre for Evidence-based Medicine level of evidence/grade</th>
<th>AGO recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>2b A</td>
</tr>
<tr>
<td>TAC</td>
<td>2b B</td>
</tr>
<tr>
<td>AP-CMF</td>
<td>2b B</td>
</tr>
<tr>
<td>P weekly→FAC</td>
<td>2b B</td>
</tr>
<tr>
<td>Dose-dense E→P</td>
<td>2b B</td>
</tr>
</tbody>
</table>

*Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need to be worrisome, and not all worrisome heterogeneity need be statistically significant.

Oxford levels of evidence: 2b = Individual cohort study [including low quality RCT (randomized controlled trial); e.g. <80% follow-up].
Grade of recommendation A = consistent level 1 studies.
Grade of recommendation B = consistent level 2 or 3 studies or extrapolations from level 1 studies.
Abbreviations: A, adriamycin (doxorubicin); C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; M, methotrexate; P, paclitaxel; T, docetaxel.

docetaxel sequential to AC was superior to AC alone. The pCR and complete or partial clinical response rates (primary endpoints) were significantly higher in patients who received docetaxel-containing chemotherapy than in those receiving standard anthracycline-based chemotherapy, as was the overall clinical response rate (complete plus partial responses) (91% versus 86%; P < 0.001). In a most recent analysis, recurrence-free survival was significantly superior for the neo-adjuvant sequence of AC and docetaxel compared with docetaxel alone (HR 0.83; P = 0.04) [13].

The GEPARDUO trial [14] compared the efficacy of four cycles of docorubicin 50 mg/m² plus docetaxel 75 mg/m² administered every 2 weeks (n = 451) with the same AC–docetaxel regimen of NSABP B-27 (n = 453) in women with operable breast cancer [10]. Results show a significantly higher pCR rate (breast and axillary nodes) with docetaxel sequential to AC than dose-dense doxorubicin plus docetaxel (14% versus 7%; P < 0.001) [10]. The overall response rate detected by imaging was also significantly higher [79% versus 69%; P < 0.001 (n = 863)], as was the breast conservation surgery rate [75% versus 66%; P < 0.005 (n = 885)]. Until now no difference in survival has been found [15].

Further improvement of the AC followed by docetaxel sequence was the aim of the GeparQuattro trial [16]. A total of 1510 patients were treated with four cycles of epirubicin–cyclophosphamide and then randomized to either four cycles of docetaxel 100 mg/m², four cycles of a combination of docetaxel 75 mg/m² and capcitabine 1800 mg/m² (given for 14 days) or a sequence of four cycles of docetaxel followed by four cycles of capicitabine at the same doses. No difference in pCR, clinical response or breast conservation rates were observed.

The European Cooperative Trial in Operable breast cancer (ECTO) [17] randomly tested whether efficacy of adjuvant doxorubicin followed by i.v. CMF (CMF; doxorubicin→CMF, arm A) could be improved by adding paclitaxel (docorubicin/paclitaxel→CMF) as adjuvant (arm B) or primary systemic therapy (PST, arm C). The clinical complete and partial remission rate of the 1355 participating women was 78%, with an in-breast pCR rate (including non-invasive residuals) of 23% and an in-breast plus lymph node pCR rate of 20%. After a median follow-up of 43 months, freedom from progression was significantly better for women receiving adjuvant AT→CMF (arms B + C) than A→CMF (arm A) (HR 0.65, range 0.48–0.90, P = 0.01). PFS was not statistically different between patients receiving AT→CMF as adjuvant (arm B) or as neo-adjuvant (arm C) treatment (HR 0.83, range 0.59–1.16, P = 0.27).

The German AGO group [18] designed a study to compare two epirubicin- and paclitaxel-containing regimens given either as dose-dense sequential chemotherapy [3× epirubicin 150 mg/m² followed by 3× paclitaxel 250 mg/m² q2w with granulocyte-colony stimulating factor (G-CSF)] or in a standard dose (4× epirubicin/paclitaxel 90/175 mg/m² q3w). The pCR (including non-invasive residuals) rate was 19% after the dose-dense and 10% after the conventional treatment (P = 0.03). Superior outcome was also demonstrated by a higher breast conservation rate (61% versus 50%) as well as in an improved rate of DFS (70% versus 59%, P = 0.011) and overall survival (83% versus 77%, P = 0.041) at 5 years.

The only large-scale trial exploring an anthracycline–taxane combination is the Gepartrio study of the GBG [19, 20]. A total of 2106 patients started neo-adjuvant treatment with two cycles of TAC. Response of the primary tumor was thereafter evaluated by sonography. Further systemic treatment was discontinued in 79 patients due to toxicity, tumor progression, patient’s wish or other reason; 1390 (66.5%) patients were randomized as responders after two initial cycles to receive four (n = 704) or six (n = 686) further TAC cycles. pCR rates were 21.0% (95% CI 18.1–24.2%) and 23.5% (95% CI 20.3–26.8%), respectively (two-sided P = 0.27). Six hundred twenty-two (29.8%) patients were randomized as non-responders to either continuation of TAC for a further four cycles or a switch to a non-cross-resistant combination of NX. Sonographic response rate was 50.5% for 321 patients randomized to further TAC and 51.2% for 301 patients randomized to NX (difference NX–TAC 0.7%, 95% CI –7.2–8.6%, proving non-inferiority (difference ≥10%) of NX, two-sided P = 0.008). BCS was possible in 57.3% and 59.8% and pCR was diagnosed in 5.3% and 6.0%, respectively.

Based on this evidence, the German AGO guidelines recommend AC→T (doxorubicin, cyclophosphamide followed by docetaxel), TAC (docetaxel, doxorubicin, cyclophosphamide) and AP-CMF (doxorubicin, paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil) for their use in routine practice [21].

Promising results of high pCR rates have been reported recently for weekly administration of paclitaxel, and for the addition of the anti-HER2 (human epidermal growth factor receptor-2) monoclonal antibody, trastuzumab, to cytotoxic therapy in patients with HER2/neu overexpressing tumors. However, confirmation of these results in large controlled trials is required [22, 23].
disclosures

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references


13. Wolmark N. NCI Consensus Meeting on PST, Bethesda 2007 (oral communication).


