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Neoadjuvant breast cancer therapy: the German experience

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ABSTRACT

Neoadjuvant systemic chemotherapy (NST) can effect freedom from locoregional and distant disease, improve surgical options by reducing the extent of required surgery, and provide useful early information on tumour biology and responsiveness to chemotherapy. Taxane-containing regimens are widely used both as monotherapy and in combination with anthracyclines. However, questions remain regarding choice of agents, optimal treatment duration and whether sequential or simultaneous administration of these agents is best. In future NST may be tailored to optimise treatment for individual patients, based upon improved knowledge of the efficacy and tolerability of different chemotherapy regimens and the prognostic significance of pathologic complete remission and/or other markers of likely response to therapy.

1. Introduction

Primary breast cancer is now regarded as a systemic disease with a locoregional component. Thus, systemic treatment comprises a fundamental component of the treatment of patients with this malignancy. Pre- or postoperative administration of cytotoxic therapy have similar efficacy in this setting.[1] Consequently, preoperative neoadjuvant systemic therapy (NST) is now widely accepted as an approach that can meet three fundamental aims of therapy by (1) obtaining freedom from locoregional and distant disease, (2) improving surgical options by reducing the extent of required surgery, and (3) providing useful early information on tumour biology and responsiveness to chemotherapy.[2]

This paper highlights the German experience with neoadjuvant breast cancer therapy and focuses on the evidence-based and annually reviewed recommendations for neoadjuvant breast cancer therapy of the German Arbeitsgemeinschaft Gynäkologische Onkologie (AGO).[3] The international recommendations of neoadjuvant trialists are also considered.[2]

2. Candidates for NST

NST followed by surgery has not been directly compared with surgery alone in large scale clinical trials. However, there is a significant body of evidence to support the use of NST in patients with operable breast cancer, and this evidence has been evaluated by an International Expert Panel.[2] Thus, primary NST is now well established and widely accepted as one of the standard treatments for patients with operable primary 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 tumours, 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 NST 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;

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- those who can undergo a lumpectomy but whose physical appearance may be less damaged if NST is given first;
- those who wish to take advantage of a response assessment of their tumour before it is removed. A demonstrable response to NST 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, NST 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 NST 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 (approximately 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.[4]

Until now, there have been no data that accurately define which patients with oestrogen receptor (ER)-positive disease must have neoadjuvant chemotherapy and which ones can just have endocrine therapy. Current research efforts aim to identify molecular markers at surgery that predict long term efficacy of neoadjuvant/adjuvant endocrine treatment. At present, there are no data on the comparative efficacy of hormonal treatments administered pre- and postoperatively. Comparing different endocrine approaches, 3–4 months' treatment with an aromatase inhibitor reaches the highest efficacy in terms of clinical response. However, the reported pCR rates are as low as 2%.

3. Freedom from disease

NST is considered to be as safe and effective as adjuvant therapy based on several randomised trials demonstrating similar survival rates after neoadjuvant and adjuvant treatment.[5–7] A European Organisation for Research and Treatment of Cancer study in 698 patients showed similar progressions-free survival (65% versus 70%) and overall survival (OS; 82% versus 84%) rates at a median of 56 months when FEC (5-fluorouracil, epirubicin, cyclophosphamide) chemotherapy was administered either pre- or postoperatively, respectively.[1] The US National Surgical Adjuvant Breast and Bowel (NSABP) B-18 study in 1523 patients showed the same 5-year disease-free survival (DFS; 67% versus 67%) and OS (80% versus 80%) rates with neoadjuvant versus adjuvant AC (doxorubicin plus cyclophosphamide) therapy.[8] In another trial, 390 premenopausal evaluable patients with tumours too large for breast conserving surgery (BCS) received either four cycles of neoadjuvant cyclophosphamide, doxorubicin, 5-fluorouracil followed by locoregional treatment or four cycles of adjuvant chemotherapy after radiotherapy.[9] At a median follow-up of 54 months there was a statistically significant (P = 0.039) difference in survival in favour of neoadjuvant therapy and a similar trend for time to metastatic recurrence. However, the authors noted that the slightly more aggressive therapy in the neoadjuvant arm may have influenced these findings.

In assessing the effectiveness of NST, the pCR in removed breast and axillary tissue is considered indicative of complete eradication of locoregional 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 NST.[10,11] In the large NSABP-27 trial of 2411 women with operable breast cancer, analysis of the 7-year follow-up data showed that pCR was a highly significant predictor of improved DFS (hazard ratio = 0.45, P = <0.0001) and OS (hazard ratio = 0.33, 95% confidence interval [CI] 0.23, 0.47; P = <0.0001).[12]

Anthracycline/taxane-based chemotherapy regimens are the most widely prescribed for NST in patients with operable breast cancer. Currently, the German AGO guidelines recommend five treatment regimens (Table 1).[3] Three of these regimens (AC→T [doxorubicin, cyclophosphamide followed by docetaxel], TAC [docetaxel, doxorubicin, cyclophosphamide] and AP-CMF [doxorubicin, paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil]) have been explored extensively in phase III trials and therefore have a higher level of evidence supporting their use.[3] A number of different approaches to the administration of these combination regimens have been tested including sequential and concurrent administration and dose-dense regimens. However, to date, no strategy has been proven superior to the others.

A problem with the use of taxane-containing regimens is the potential for haematological toxicity. For example, the Breast Cancer International Research Group 001 investigators found that grade 3–4 neutropenia occurred in 66% and febrile neutropenia (FN) in 25% of 745 patients receiving TAC adjuvant therapy without granulocyte colony-stimulating factor (G-CSF) support.[13] In this regard, data from the GeparTrio study showed that neoadjuvant taxane-containing therapy can be administered without undue concerns over haematological toxicity if appropriate G-CSF prophylaxis is used.[14] Treatment was given to sequential patient cohorts with three different supportive regimens throughout the conduct of the trial. In this study in patients receiving NST with the TAC regimen, the incidence of FN was 6% in 311 patients who received primary prophylaxis with pegfilgrastim compared with 17% in those (n = 385) who received daily G-CSF (filgrastim or lenograstim) and 5% in patients (219) who received ciprofloxacin and pegfilgrastim. Interestingly, pegfilgrastim (once-per-cycle administration) significantly reduced the incidence of FN compared with daily G-CSF (65% relative risk reduction; $P < 0.001$).[14]

The toxicity of taxane-containing regimens has resulted in a reluctance to prescribe these agents in elderly patients, who may be at significant risk for myelosuppression in particular. However, an integrated analysis of four large clinical trials has indicated that toxicity in elderly patients (here defined as aged >60 years) does not differ significantly from that in younger patients.[15] Thus, with appropriate primary prophylaxis with G-CSF, anthracycline-taxane regimens can also be considered for NST in otherwise fit elderly patients.

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

Table 1 – Neoadjuvant treatment regimens for breast cancer recommended by German Arbeitsgemeinschaft Gynäkologische Onkologie

	Oxford Centre for Evidence-based Medicine Level of evidence/grade	AGO recommendation
AC → T	2b * A	+
TAC	2b B	+
AP-CMF	2b B	+
P weekly → FAC	2b B	+/–
Dose-dense E → P	2b B	+/–

Abbreviations: A, adriamycin (doxorubicin); C, cyclophosphamide; T, docetaxel; P, paclitaxel; M, methotrexate; F, 5-fluorouracil; E, epirubicin.
Oxford levels of evidence
2b = Individual cohort study (including low quality RCT [randomised controlled trial]; e.g. <80% follow-up).
* 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 be worrisome, and not all worrisome heterogeneity need be statistically significant.
Grade of recommendation A = consistent level 1 studies.
Grade of recommendation B = consistent level 2 or 3 studies or extrapolations from level 1 studies.

receptor-2) monoclonal antibody, trastuzumab, to cytotoxic therapy (discussed below) in patients with HER2/neu over-expressing tumours. However, confirmation of these results in large controlled trials is required.

4. Improving surgical options

Significant improvements in breast conservation have been observed with the use of neoadjuvant chemotherapy (Table 2).[9,16–22] For example, in the NSABP-B27 study, 62% of patients who received preoperative chemotherapy with AC (n = 1533) and 64% of those who received NST with AC-T (n = 722) had successful BCS.[19] Among patients who had a clinical complete response (cCR) to NST, 70% underwent lumpectomies, compared with 56% of those without a cCR ($P < 0.001$). For patients with a pCR, 71% underwent BCS compared with 60% of those with invasive cancer in the breast ($P < 0.001$). In the GeparTrio pilot study, including 16% of patients with T4 a–d tumours, BCS was possible in 72% of patients overall.[22] 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 NST are candidates for BCS. To aid patient selection for BCS after NST, a series of selection criteria have been developed,[23] and a prognostic index for in-breast and locoregional recurrence.[24] Each indicator is given a score of 1, and a low score (0–1) has a good prognosis with few breast or loco-regional recurrences; a high score (3–4) has a poor prognosis with over 40% breast or loco-regional recurrences. Locoregional recurrence comprises clinical N2 and N3 status, residual pathological tumour size >2 cm, lymphovascular 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 is remains unclear if this initial benefit of higher BCS can be maintained.

Sentinel lymph node (SLN) biopsy after neoadjuvant therapy is commonly accepted for patients with primary T1–2, N0, M0 tumours. Available data show it to have an identification rate ranging from 77–98%, accuracy in the range 77–100% and a false-negative rate of up to 33%.[25] The data on the efficacy and feasibility of SLN biopsy are inconsistent due to the small numbers of patients enrolled in the

Table 2 – Breast conservation rates after neoadjuvant therapy

Trial	n	Treatment	Breast conservation rate (%)		
			Adjuvant systemic chemotherapy	Neoadjuvant chemotherapy-1	Neoadjuvant chemotherapy-2
NSABP B-18[16]	1523	AC	60	67	–
ECTO[17]	1355	AP-CMF	34	65	–
EORTC[18]	448	FEC	21	37	–
Scholl[9]	414	FAC	77	82	75
NSABP B-27[19]	2411	AC/AC-D	–	61	61
AGO[20]	631	EP/E-P	–	50	63
Geparduo[21]	913	ADdd/AC-D	–	66	75
Gepartrio (pilot)[22]	286	DAC/DAC-NX	–	–	81

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; ECTO, European Cooperative Trial in Operable breast cancer; EORTC, European Organisation for Research and Treatment of Cancer; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie (Gynecologic Oncology Working Group); A, doxorubicin; E, epirubicin; P, paclitaxel; D, docetaxel; M, methotrexate; F, 5-fluorouracil; C, cyclophosphamide; N, vinorelbine; X, capecitabine.

single centre trials conducted to date. Given adequate experience and standardization of the technique, SLN biopsy after NST can be regarded as an option for patients who have shown a response to NST but not for those with inflammatory disease.[26] The requirement for SLN biopsy before NST is debatable.

5. Information on response and biology of disease

The identification of immunohistochemical and gene markers and response to initial NST are under investigation as possible predictive factors for response to therapy. With regard to the first approach, negative hormone receptor (HR) status has emerged as the strongest predictive factor identified to date. In the NSABP-27 study, overall, ER-negative patients had a better response to NST compared with ER-positive patients.[19] However, ER status had little effect on the ability of preoperative docetaxel to improve pathologic response. In the GeparTrio pilot study in 285 patients,[22] the pCR rate was just 3% in patients aged >35 years with well differentiated, HR-positive T2 tumours but no clinical lymph node involvement. Consequently, this group has not been included in the main trial. The pCR rates in the main GeparTrio study for patients with known ER/progesterone-(Prog)R status were as follows: –/– 34% (*n* = 629); +/– 12% (*n* = 266) and +/+ 6% (*n* = 900).[27] Interestingly, patients who were HER2-positive or HER2-negative had similar pCR rates in response to treatment (17% [*n* = 282] versus 18% [*n* = 1319]).[27] The highest pCR rates in this trial were recorded for patients with triple-negative tumours (ER/ProgR/HER2) i.e. 41% (*n* = 327) in contrast to 29% (–/–/+, *n* = 172) and 8% (all other combinations, *n* = 935).[27] These recent results indicate that negative HR status is a strong predictive factor for response to treatment.

The use of gene profiles to predict pCR is very labour intensive and must be considered experimental at this point in time. Data from a small pilot study indicate that patients with tumours over-expressing the ErbB-2 gene achieve very high (>60%) pCR rates when trastuzumab is added to FEC or paclitaxel-containing NST.[28] This approach is likely to be particularly effective in young patients and those with inflammatory disease who more commonly over-express this gene. Data from another study[29] indicated that the subset of patients with ER-positive disease over-expressing ErbB-1 and/or ErbB-2 responded better to letrozole than to tamoxifen. Predictive factors for response to endocrine therapy are HR status and possibly HER2/neu status. Gene expression profiles and the immunohistological distinction between basal-like and luminal-like tumours have been suggested to have good predictive value.[30] However, further investigation is required.

Based on the observed predictive relationship between locoregional response and patient outcomes, it has been suggested that assessment of response to NST could be used as a predictive factor to modify subsequent therapy for individual patients. Response to NST may also help investigate markers that could be used to optimize therapy for individual patients. 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.[22,31,32] Fig. 1 shows the study design and treatment regimens. Patients with untreated breast cancer initially received two cycles of TAC NST and were assessed for response. Then, patients with a clinical response were randomised to receive either four (*n* = 704) or six (*n* = 686) further cycles of TAC. Patients with no response to the initial treatment were randomised to receive either four more cycles of TAC (*n* = 321) or NX (vinorelbine, capecitabine; *n* = 301). Most patients received G-CSF support. As shown in Fig. 2, 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, in-

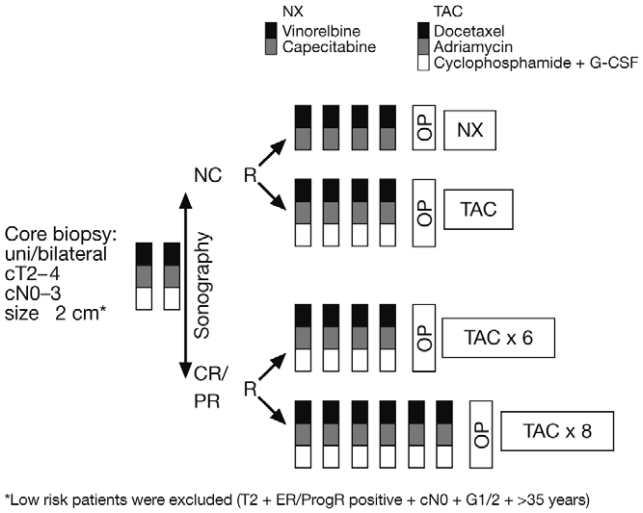

Fig. 1 – GeparTrio study design. *Abbreviations:* G-CSF, granulocyte-colony stimulating factor; T, tumour size and location and N, regional lymph node involvement according to the TN classification system; NC, no clinical response; CR, complete response; PR, partial response; R, randomisation; OP, operation (surgery); ER, oestrogen receptor; ProgR, progesterone receptor.

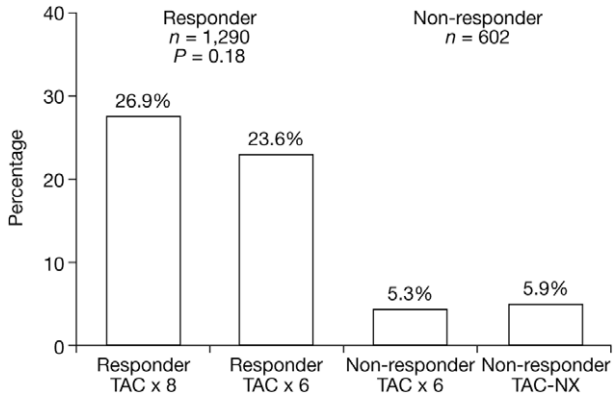

Fig. 2 – Pathologic complete remission in GeparTrio. *Abbreviations:* TAC, docetaxel, doxorubicin, cyclophosphamide; NX, vinorelbine, capecitabine.

Table 3 – Significant predictive factors for pathological complete remission in the GeparTrio study (multivariate analysis)[27]

Parameter	Odds ratio*		
	All patients $n = 1210$	Responders $n = 831$	Non-responders $n = 370$
<40 years	2.0	–	6.3
Tumour grade (3 versus 1 + 2)	2.7	2.2	–
Tumor type (ductal versus other)	2.2	2.1	–
ER/ProgR (negative versus positive	3.7	4.3	2.5
Complete response after 2 cycles	10.4	2.3	NA

*Odds ratio against group with lowest pathological complete remission rate.
Abbreviations: ER, oestrogen receptor; ProgR, progesterone receptor; NA, not applicable.

cluding those switched to NX therapy. Multivariate analysis of the GeparTrio results (Table 3) identified ER status as having a predictive value for achieving a pCR, with ER-negative patients having a greater chance of a pCR than receptor-positive patients. These data indicate that initial response to NST does have predictive value for overall response to therapy.

The prospective, randomised, phase III GeparQuattro study investigates whether the amount/type of drug or duration of treatment improves the pCR rate. Following four cycles of EC, patients will be randomised to one of three groups to assess the effects of (1) docetaxel monotherapy for four cycles, (2) docetaxel with capecitabine for four cycles, and (3) docetaxel (four cycles) followed by capecitabine (four cycles), all prior to surgery. Patients with HER2-positive tumours received trastuzumab throughout all neoadjuvant chemotherapy. Recruitment of 1500 patients to this study was completed in December 2006 and data will first be available end of 2007.

It remains uncertain how to proceed with patients having involved lymph nodes with or without remaining disease in the breast after NST. These patients have a considerable risk for relapse. Endocrine and/or anti HER2 treatment will be provided in the case of hormone sensitive and/or HER2-positive disease. Studies addressing the use of bisphosphonates or antiangiogenic agents are currently underway (NaTaN-study) or in preparation (NSABP-study).

6. Summary

Equivalent survival rates are obtained after neoadjuvant and adjuvant therapy with the same regimen. However, NST has the added benefit of improving surgical options, thereby allowing more BCS to be performed. Response to NST is predictive of long-term outcome and pCR is strongly associated with improved DFS and OS. However, it remains to be seen whether or not increasing pCR rates with administration of more active NST regimens can improve OS. At present, doxorubicin-taxane based NST regimens show the highest efficacy; although the optimal regimen and schedule has yet to be determined. The tailoring of NST to optimise treatment for individual patients may be achieved through improved knowledge of (1) the efficacy and tolerability of different chemotherapy regimens, (2) the prognostic significance of pCR and/or (3) other markers of likely response to therapy (including biological markers).

7. Conflict of interest statement

Gunter von Minckwitz has received grants for the conduct of the studies from Sanofi-Aventis, Roche and Amgen. Sibylle Loibl has no potential conflict of interest to declare. Manfred Kaufmann has no potential conflict of interest to declare.

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