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Clinical response by palpation during primary systemic therapy with four dose-dense cycles doxorubicin and docetaxel in patients with operable breast cancer: Further results from a randomised controlled trial

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ABSTRACT

Primary systemic therapy (PST) allows the observation of tumour response under treatment, but little is known regarding the typical course of clinical response during such therapy. The aim of this study is to support decision making in case of insufficient clinical response. Tumour response was assessed by palpation at different times in 436 patients with operable breast cancer from the dose-dense biweekly therapy arm of the GEPARDUO phase III trial. The predictive value of clinical response for pathologic complete response (pCR), prognostic models to assess the prognosis and individual courses of clinical response were investigated. Sensitivity and positive predictive value were low, but comparatively highest after the 3rd cycle. The predictive value of clinical response by palpation for pCR was subsequently limited. The majority of patients (68.1%) experienced a consistent decrease in tumour size during PST. The results indicate that decisions about further treatment should take place at the earliest after the 3rd cycle or 6 weeks of dose-dense PST.

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1. Introduction

Primary systemic therapy (PST) was initially given to breast cancer patients with inoperable locally advanced breast cancer or inflammatory breast cancer,[1–4] and may be considered as standard treatment for these patients. In patients with operable breast cancer, PST results in higher rates of breast conserving therapy and is increasingly applied.[5] An advantage in survival over adjuvant systemic therapy (AST) has not been demonstrated so far.[6–9] Pathologic complete response (pCR) was the primary end-point of the GEPARDUO study,[10] a phase III trial comparing a dose-dense biweekly to a sequential 3 weekly chemoendocrine therapy regimen in women with operable breast cancer. Since it is correlated with improved survival,[4,7,9] pCR can be viewed as an intermediate end-point for survival. Conflicting results from two studies show no association of pCR and clinical response and thus, a less accurate prediction of survival by clinical response compared to pCR.[11,12] In both studies additional AST has been administered, and the number of pCRs was low, which might have influenced the results. In contrast to AST, PST (or neoadjuvant therapy) allows the observation of clinical response of both primary breast tumour and axillary lymph nodes under treatment, serving as an *in vivo* chemosensitivity test. Investigation of the clinical response to PST may help to identify and assess factors influencing pathological response. One possible clinical parameter is tumour size measurement by palpation.

Little has been reported on the change in tumour size during the course of PST, and the ability of such a change to predict pCR. Interest has been focused on adapting PST based on clinical response. Two large randomised trials on PST, the GEPARTRIO trial[13] and the Aberdeen Tax301 trial,[14–16] administered salvage therapy regimens in case of not achieving a clinical response by palpation or sonography. This approach relies on the assumption that clinical response after a couple of chemotherapy cycles is a valid predictor of pathological response and of survival. Our study aimed to assess this assumption by analysing the data on tumour palpation at different times during PST for the ADOC (doxorubicin, docetaxel and tamoxifen) therapy arm patients in the GEPARDUO trial.[10] This trial also included an evaluation of the predictive values of clinical response by palpation and sonography directly before surgery for achieving a pCR for both treatment arms together.[10] However, the clinical relevance of clinical response pre-surgery is limited as it cannot be used as a guide for further treatment, i.e. both systemic and loco-regional treatment.

We therefore assessed the predictive values of clinical response for achieving a pCR at different points in time during PST. For an overall assessment of the accuracy of the prognoses in the time course, we investigated univariate and multivariate prognostic models for each point in time. Additionally, we analysed the individual courses of clinical response by palpation to generate hypotheses on the pattern of clinical response during PST. These investigations were additional exploratory analyses within the GEPARDUO trial.

2. Patients and methods

2.1. Patients

Our study included all patients from the ADOC therapy arm of the GEPARDUO trial for whom data on palpation were available. The selection criteria are those described in the initial trial.[10] Patients were aged $\geqslant$18 years and had unilateral, histologically proven, invasive, operable adenocarcinoma of the breast (T2-3, N0-2, M0), with primary tumour bi-dimensionally measurable and Karnofsky performance status $\geqslant$70%. We excluded patients with bilateral breast cancer, any previous treatment for breast cancer, any previous treatment with cytotoxic agents and any previous malignancy other than breast cancer.

2.2. Treatment

Patients randomly assigned to the dose-dense ADOC treatment arm received doxorubicin 50 mg/m^2 followed by docetaxel 75 mg/m^2 on day 1 every 14 days for 4 cycles. Prophylactic granulocyte colony-stimulating factor (G-CSF) was administered from days 5 to 10. All patients received 20 mg tamoxifen/day from day 1 until surgery. Patients with hormone receptor positive tumours got tamoxifen for 5 years postoperative or until disease relapse.

2.3. Assessments

Baseline evaluation, including a complete tumour assessment, was performed within 4 weeks before randomisation. The primary tumour was then evaluated clinically by palpation after each of the 4 cycles of PST, the fourth being directly before surgery (five assessments in total). Surgery was performed within 14–28 days after the last application of ADOC.

2.4. End-points

The primary aim of this investigation was to assess the predictive value of clinical response for pCR at different times during PST. Clinical tumour response by palpation was classified as follows: clinical complete response (cCR), complete disappearance of all detectable malignant disease in breast; clinical partial response (cPR), reduction of the primary tumour size of 50% or more; clinical stable disease (cSD), less than 50% reduction of tumour size until less than 25% increase of tumour size; clinical progressive disease (cPD), increase of tumour size of 25% or more and/or detection of new lesions, compared to baseline. With clinical response (cR) we denote the category 'cCR or cPR'. We considered clinical tumour size as the product of the two largest perpendicular diameters of the primary tumour. The definition for pCR was regression grade 4 according to Sinn and colleagues[17]: complete invasive and non-invasive pathologic response. Here, we focused on the pCR of the breast because the definition of clinical response did not include clinical axillary node response. In the initial study,[10] the primary end-point was pCR of breast and axilla. A further aim was to generate hypotheses on the pattern of clinical response during PST by analysing the individual courses of clinical response.

2.5. Statistics

Relative frequencies of clinical response categories at different times were calculated for all patients with values on clinical response available. We investigated different predictive models for pCR for each point in time: logistic regression with relative change of tumour size as explanatory variable on different measurement scales with and without standard prognostic factors (age, tumour size, hormone receptor status and clinical nodal status). To assess these models, the mean squared difference between model-based probability predictions and binary pCR outcome (Brier score) was calculated for each time as summary measure for the prediction error.[18,19] These errors were compared to the prediction errors of a benchmark prediction given by the prevalence of pCR. In addition, we defined six patterns of individual courses of clinical response using the sequence of responses after each of the four PST cycles: consistent decrease; consistent increase; constant course (cSD for each assessment); decrease then increase; increase then decrease; at least two alterations (Table 1).

Full local ethics committee approval was obtained at all participating centres and the GEPARDUO study adhered fully with the Declaration of Helsinki. All patients gave written informed consent.

3. Results

3.1. Baseline results and patient characteristics

The full efficacy population (FEP) in the ADOC arm of the GEPARDUO trial consisted of 444 patients. Baseline results and patient characteristics have already been published in detail.[10] Since there were not enough data on palpation for eight patients in the FEP, our study population included 436 patients. For 91% of these patients, data on palpation were available from at least 4 assessments: 338 patients (77.5%) from all 5 assessments and 58 patients (13.3%) from 4 assessments.

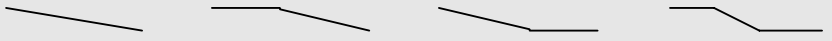
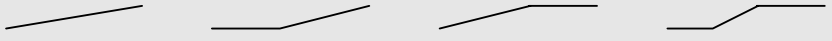
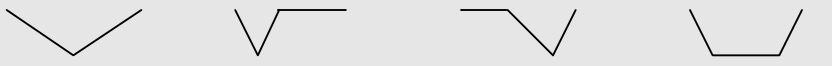
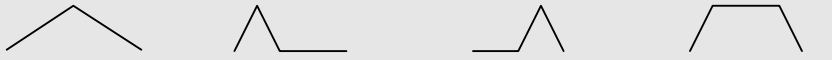
3.2. Clinical response by palpation per therapy cycle

The clinical responses per therapy cycle are displayed in Fig. 1. The rate of patients with a cCR increased consistently during PST, whereas the rate of patients with a cSD decreased consistently. The cPD rate reached a peak of 6.0% after the 1st cycle of PST, and remained constantly low from the 2nd cycle onwards with rates ranging from 3.8% after the 2nd cycle to 2.7% after the 3rd cycle. One hundred and 36 patients (31.2%) reached a cCR after the last PST cycle. Only 55 of these have already shown a cCR after the 3rd cycle, whereas 74 patients reached the cCR as recently as during the last cycle. For 7 patients the assessment after the 3rd cycle was missing.

3.3. Predictive values for complete pathologic response

The predictive values for a pCR in the breast, based on cCR and on cR, are shown in Table 2. The sensitivity (Sens) based on cCR was low during the first 2 cycles. The greatest increase was from the end of the 2nd cycle (9.1%) to the end of the 3rd cycle (46.9%). The specificity (Spec) based on cCR kept a high level throughout PST. The comparatively greatest decrease in Spec was between the end of the 3rd cycle (87.2%) and the end of the 4th cycle (71.5%). The Sens based on cR was notably higher, the Spec accordingly lower than the respective values based on cCR. The positive predictive values (PPV) were low at any measuring time during PST, especially based on cR. The highest value was reached after the 3rd cycle (23.8%) based on cCR. The negative predictive value (NPV) was con-

Table 1 – Clinical response: graphs of possible courses

Course of clinical response (example)	Possible courses of response
Consistent decrease (cSD, cSD, cPR, cCR)	
Consistent increase (cSD, cSD, cSD, cPD)	
Constant course (cSD, cSD, cSD, cSD)	
Decrease → increase (cSD, cSD, cPR, cSD)	
Increase → decrease (cPD, cSD, cPR, cCR)	
At least two alterations (cPR, cSD, cCR, cPD)	

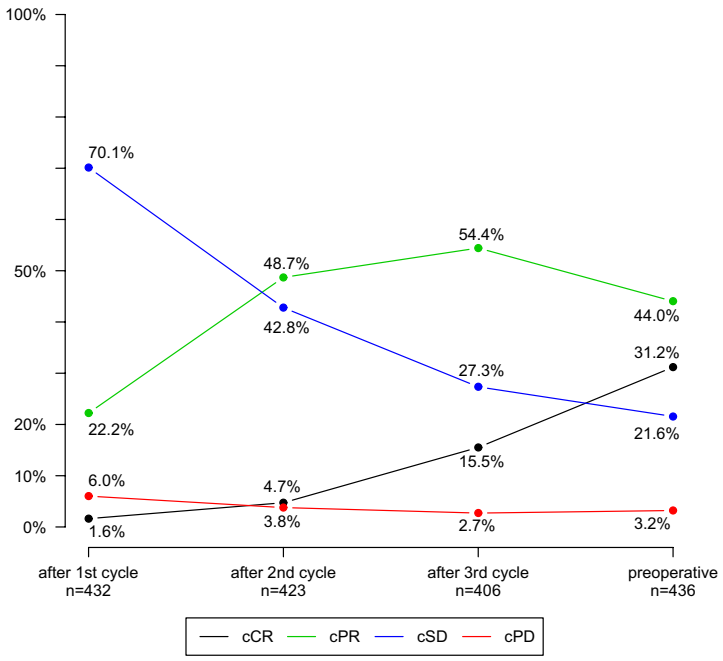


Fig. 1 – Percentage of patients with specific clinical response category in the time course: cCR, clinical complete response; cPR, clinical partial response; cSD, clinical stable disease; cPD, clinical progressive disease.

Table 2 – Predictive values for a pCR in breast at different points in time

Time point after	*n* (pCR)	cCR (pCR)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PEa	PEb
1st cycle PST	432 (33)	7 (1)	3.0	98.5	14.3	92.5	0.0705	0.0584
2nd cycle PST	423 (33)	20 (3)	9.1	95.6	15.0	92.6	0.0717	0.0573
3rd cycle PST	406 (32)	63 (15)	46.9	87.2	23.8	95.0	0.0679	0.0516
4th cycle PST	436 (33)	136 (21)	63.6	71.5	15.4	96.0	0.0672	0.0548
	n (pCR)	cR (pCR)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PEa	PEb
1st cycle PST	432 (33)	103 (8)	24.2	76.2	7.8	92.4	0.0705	0.0590
2nd cycle PST	423 (33)	226 (20)	60.6	47.2	8.9	93.4	0.0718	0.0591
3rd cycle PST	406 (32)	284 (24)	75.0	30.5	8.5	93.4	0.0725	0.0609
4th cycle PST	436 (33)	328 (31)	93.9	26.3	9.5	98.1	0.0689	0.0576

pCR, pathologic complete response; cCR, clinical complete response; cR, clinical response; PST, primary systemic therapy; *n*, number; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; PEa, prediction error in model including only clinical tumour response; PEb, prediction error in model including clinical tumour response and additional standard prognostic factors.

stantly high during PST. The numbers of true positives (15), true negatives (326), false positives (48) and false negatives (17) for the prediction of pCR after 3 cycles of PST are displayed in Table 3. The respective tables for the other points in time may be calculated based on the numbers given in Table 2. The prediction errors (Table 2) were altogether small in the models under investigation, including the benchmark prediction (prevalence of pCR: benchmark prediction error = 0.0726) where the prediction error was below 0.08 at all times. This is typical for a situation with rare outcomes (few pCRs) where even a trivial prediction (no pCR at all) would be correct in the majority of cases. The consideration of the model based prediction error in the course of time supports the above results as far as the predictive value of cCR is concerned: the prediction error was smallest after the 3rd PST cycle (0.0679 for the model including only clinical tumour response, 0.0516 with additional prognostic factors), i.e. with respect to prediction, information from this point in time was

Table 3 – 2 × 2 table cCR/pCR in breast after 3rd cycle PST

	No pCR	pCR	Total
No cCR	True neg: 326	False neg: 17	343
cCR	False pos: 48	True pos: 15	63
Total	374	32	406

cCR, clinical complete response; pCR, pathologic complete response; PST, primary systemic therapy; True neg, true negative; False neg, false negative; False pos, false positive; True pos, true positive.

best (Table 2). Regarding the comparison to the benchmark prediction the improvement was negligibly low (6%) in models including only complete clinical tumour response. In models with additional prognostic factors, however, the prediction error was reduced by about 30% in comparison to the benchmark.

An additional analysis of the predictive value of a cCR in breast for a pCR in both breast and axillary lymph nodes resulted in only marginal differences of the predictive values (results not shown).

Predictive values for pCR by oestrogen receptor (ER) status (ER+ versus ER–) and by age (Age $\leqslant$ 50 versus Age > 50) after the 3rd cycle for cCR and cR are displayed in Table 4. No pronounced effect of age regarding the predictive values can be seen. Pertaining to the predictive values by ER status, there is no substantial difference of Sens, Spec and NPV. Although Sens is only slightly larger, PPV is considerably higher in ER– patients (Table 4) which is due to the fact that the prevalence, i.e. the pCR rate, is much higher in this subgroup.

3.4. *Course of clinical response in individual patients*

The courses of clinical response and the respective pCR rates are shown in Table 5. We classified the individual course of clinical response by palpation for 433 patients (99.3%). For 3 patients with only one assessment a classification was not possible.

The majority of patients, 297 out of 433 patients (68.1%), showed a consistent decrease in tumour size during PST, and 52 patients (11.9%) had a constant course of clinical response. Forty-three patients (9.9%) experienced an initial decrease followed by an increase in tumour size, where most frequently the individual courses consisted of only two categories: cSD and cPR (28 patients, 65.1%). Five (11.6%) of the patients with course 'decrease then increase' had a cPD during PST, but only at the preoperative assessment. Eight patients (18.6%) had a cCR at least once during the earlier assessments, but did not achieve a cCR at the preoperative assessment.

There were 42 patients with a cPD at least once during PST. The numbers of patients with a cPD once, twice, three and four times during PST were 27 (64.3%), 8 (19.1%), 4 (9.5%) and 3 (7.1%), respectively. The majority of patients with a cPD (25 patients, 59.5%) had an initial increase followed by a decrease of clinical response, which indicates a transient disease progression. Other courses were much less frequent. Only 4 patients with cPD discontinued therapy. Three patients were assessed with cPD constantly throughout PST, but continued the PST over all four cycles.

Table 4 – Predictive values for a pCR in breast after 3rd cycle PST in different subgroups of patients

Patients with	*n* (pCR)	cCR (pCR)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
ER+	232 (4)	35 (2)	50.0	85.5	5.7	99.0
ER–	128 (24)	24 (13)	54.2	89.4	54.2	89.4
Age $\leqslant$ 50 years	199 (22)	34 (12)	54.5	87.6	35.3	93.9
Age > 50 years	207 (10)	29 (3)	30.0	86.8	10.3	96.1
	n (pCR)	cR (pCR)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
ER+	232 (4)	165 (3)	75.0	28.9	1.8	98.5
ER–	128 (24)	91 (19)	79.2	30.8	20.9	86.5
Age $\leqslant$ 50 years	199 (22)	137 (15)	68.2	31.1	10.9	88.7
Age > 50 years	207 (10)	147 (9)	90.0	29.9	6.1	98.3

pCR, pathologic complete response; cCR, clinical complete response; cR, clinical response; PST, primary systemic therapy; n, number; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; ER+, oestrogen receptor positive; ER–, oestrogen receptor negative.

Table 5 – Courses of clinical response by palpation: frequencies and pCR rates

Course of clinical response	*n*	Freq (%)[a]	*n* (pCR)	Freq (%)[b] of pCRs	pCR (%)[c]
	n = 436		*n* = 33		7.6%
Consistent decrease	297	68.1	28	84.9	9.4
Consistent increase	6	1.4	0	0.0	0.0
Constant course	52	11.9	1	3.0	1.9
Decrease → increase	43	9.9	2	6.1	4.7
Increase → Decrease	25	5.7	2	6.1	8.0
At least two alterations	10	2.3	0	0.0	0.0
Only 1 value available	3	0.7	0	0.0	0.0

n, number; freq, frequency; pCR, pathologic complete response in breast.
a % of analysis population.
b % of *n* = 33 patients with pCR.
c % of number of patients with the same course of clinical response.

The majority of patients who achieved a pCR in breast had a consistent decrease in tumour size during PST: 28 patients (84.9%) out of $n = 33$ patients. On the other hand, patients with course 'increase then decrease' achieved a pCR nearly as frequently (two patients out of 25, 8.0%) as patients with a consistent decrease in tumour size (28 patients out of 297, 9.4%). Pertaining to all other possible courses of clinical response, the pCR rates were considerably lower (Table 5).

4. Discussion

The analyses of clinical response were performed retrospectively; the interpretation of the results is subsequently limited to generate hypotheses. Our findings show that with a dose-dense biweekly, four-cycle chemoendocrine therapy regimen the positive predictive value of cCR by palpation for pCR is low. Thus, clinical response measured by palpation is not suitable to predict a pCR or to identify patients who do not need breast surgery.[10,20] Another question is if clinical response is applicable for the decision about further treatment. Compared to other points in time, cCR might best indicate when measured after the 3rd PST cycle whether a patient is a responder to PST or not. Our results suggest that if clinical response is used as a guide for further treatment, this decision should take place at the earliest before the end of the 3rd cycle, corresponding to 6 weeks.

Contrary to the strict definition of pCR as Sinn grade 4[17] in this study and several European trials,[3,9,20] the definition of pCR in some other trials on PST included non-invasive tumour residues Sinn grade 3.[4,7,11,21] An impact on the pCR rates and the predictive values of clinical response for pCR can be expected, and has to be taken into account when comparing the results.

In most large clinical trials on PST of primary breast cancer, the earliest possible decision to discontinue PST[9,10,20] or to start a non-cross resistant salvage PST regimen[13] is taken after the 2nd cycle of PST. The only trial to date, although comparatively small, using clinical response after 4 cycles as a guide for administering additional PST is the Tax301 trial conducted by the Aberdeen Breast Group.[14–16] A recent tendency is to apply therapy regimens with more than 4 cycles of PST. In this case, our findings suggest that it might be more correct to classify patients according to clinical response after 3 cycles, corresponding to 6 weeks in the present study. However, it is an open issue whether the clinical responses by palpation during PST and their ability to predict pCR are influenced by the type, length, and application interval of the therapy. We looked at the specific dose-dense therapy regimen with 2-week therapy cycles in the ADOC arm of the GEPARDUO trial.[10] All other trials used a 3-week schedule *and* different not dose-dense chemotherapy regimens,[9,13–16] except for the GEPARDO trial,[20] with a therapeutic regimen similar to the present trial. We restricted the analysis to the ADOC therapy arm, because for sequential therapy regimens that use cytotoxic agents, it would not be possible to discriminate between the effect of the number of cycles and of the specific cytotoxic agent on clinical response. The time to response with a regimen administered every 2 weeks instead of the classical 3 weeks might be shorter and might follow different cell kinetics. Therefore, further research is needed to separate the effects of time schedules from those of the applied regimen. In the AC–DOC (doxorubicin and cyclophosphamide [AC] followed by docetaxel every 3 weeks) arm of the GEPARDUO trial[10] the Sens was higher after the 2nd cycle of PST (23%) than in the ADOC arm (9%), which may point to the importance of a longer application interval. In the AC–DOC arm, the Sens after the 3rd cycle of PST is higher again and reaches a value of 30%. This result supports the findings of the investigation on hand. Nevertheless, our results do not entirely apply to conventional, not dose-dense therapy regimens.

Tamoxifen may stimulate oestrogen-induced expression of genes and may therefore influence cell proliferation and survival stimuli.[22] However, in the GEPARDO trial, tamoxifen application was not significantly correlated with the pCR rate in a dose-dense therapy setting.[20]

Baseline characteristics and the possible influence of prognostic factors on the pathological response have been reported and discussed within the original publication of the GEPARDUO trial.[10] Concerning the effect of age on the predictive values (Table 4), the contributing factor is probably the distribution of events. Regarding the cCRs, there are only three pCRs in the subgroup of patients >50 years, which might thwart the expected converse effect of the less dense mamma in older patients. The same applies to the considerably smaller PPV in ER+ compared to ER– patients, which can be explained by the low prevalence of pCR in the ER+ subgroup (Table 4). This low prevalence corresponds to the findings of several clinical trials on pathological response.[4,23,24] Summarising, the prediction error is small due to the relatively small number of events (pCRs). The alternating changes in Sens and Spec in time (Table 2) cancel each other out. This is reflected in the fact that the prediction error, which is a summary score for predictive accuracy, is almost constant in time with a minimum after the 3rd cycle of chemotherapy.

We have also found that although the cPD rate reaches a peak after the 1st cycle of PST, it stays at a constantly low level from the 2nd cycle onwards. The high proportion of 'increase then decrease' courses (60%) in patients with cPD during PST may be explained by the late onset of clinical response or in some cases by the occurrence of haematoma due to the examination at baseline. Less than 10% of patients with cPD discontinued therapy because of tumour progression.

A decrease in tumour size early during PST does not necessarily indicate that tumour size might not increase again later in the PST course; in this study, nearly every 10th patient had a course of clinical response with an increase after initial decrease.

Possible inter- and intra-observer variations can be expected to influence the assessment of clinical response considerably, which may limit the interpretation of the results. Another issue is whether different methods of assessing clinical response, such as imaging methods, could be more accurate in predicting a pathological response. As part of the GEPARTRIO trial,[13] breast ultrasound was performed in 226 out of 285 patients treated with TAC (docetaxel simultaneously with AC every 3 weeks) after 2 cycles of PST. The Sinn grade 4[17] pCR rate in patients with an imaging clinical response was 27.9% compared to 22.9% in patients with a clinical response by palpation. These results show that clinical

tumour assessment by ultrasound might predict pCR more accurately than assessment by palpation. These data were not available in the GEPARDUO trial and thus, interpretation is limited. The predictive value of clinical response during PST for pCR might be improved by combining palpation, ultrasound, mammography or magnetic resonance imaging. Until these methods are evaluated on larger populations, we will not be able to identify the best method or an optimal combination of these for predicting a pCR. In future, it may be possible to develop an effective, although more costly, combined methodology for early prediction of response to PST.

The recent tendency in breast cancer therapy by PST is towards a more individual approach that tries to identify subgroups of patients who might benefit from a specific therapy regimen. Assessing the clinical tumour response by palpation during PST may serve as one method to identify such subgroups. The subgroup of patients with a clinical tumour response 'increase then decrease' might benefit from longer therapy duration, whereas the subgroup 'decrease then increase' might benefit from a sequential therapy regimen to prevent the development of secondary drug resistance. Further studies are needed to answer these questions.

We have shown that palpation could be used to assess the response to PST with restrictions. It may support decision making (discontinuation or change of therapy) in case of insufficient clinical response after a specific number of cycles of PST. Patient and investigator could be informed which frequent patterns of courses of clinical response to PST can be anticipated, which may increase compliance with PST. Palpation is a cheap and non-invasive method without side-effects, also available in less developed settings, but it does not sufficiently predict pathological response by itself, specifically early during PST.

Conflict of interest statement

Consultant/Advisory role: Gunter von Minckwitz, Aventis; Manfred Kaufmann, Aventis; Honoria: Günter Raab, Aventis; Jörn Hilfrich, Aventis; Manfred Kaufmann, Aventis; Gunter von Minckwitz, Aventis.

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REFERENCES

1. Schick P, Goodstein J, Moor J, Butler J, Senter KL. Preoperative chemotherapy followed by mastectomy for locally advanced breast cancer. *J Surg Oncol* 1983;**22**:278–82.
2. Perloff M, Lesnick GJ. Chemotherapy before and after mastectomy in stage III breast cancer. *Arch Surg* 1982;**117**:879–81.
3. Bonadonna G, Valagussa P, Brambilla C, et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *J Clin Oncol* 1998;**16**:93–100.
4. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 1999;**17**:460–9.
5. Kaufmann M, von Minckwitz G, Smith R, et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *J Clin Oncol* 2003;**21**:2600–8.
6. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997;**15**:2483–93.
7. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;**16**:2672–85.
8. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001:96–102.
9. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001;**19**:4224–37.
10. von Minckwitz G, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO Study of the German Breast Group. *J Clin Oncol* 2005;**23**:2676–85.
11. Faneyte IF, Schrama JG, Peterse JL, et al. Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. *Br J Cancer* 2003;**88**:406–12.
12. Feldman LD, Hortobagyi GN, Buzdar AU, Ames FC, Blumenschein GR. Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res* 1986;**46**:2578–81.
13. von Minckwitz G, Blohmer JU, Raab G, et al. In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. *Ann Oncol* 2005;**16**:56–63.
14. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol* 2002;**20**:1456–66.
15. Heys SD, Hutcheon AW, Sarkar TK, et al. Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. *Clin Breast Cancer* 2002;**3**:69–74.
16. Hutcheon AW, Heys SD, Sarkar TK. Neoadjuvant docetaxel in locally advanced breast cancer. *Br Can Res Treat* 2003;**79**:19–24.
17. Sinn HP, Schmid H, Junkermann H, et al. Histological regression of breast cancer after primary (neoadjuvant) chemotherapy. *Geburtsh Frauenheilk* 1994;**54**:552–8.
18. Mussurakis S, Buckley DL, Horsman A. Prediction of axillary lymph node status in invasive breast cancer with dynamic contrast-enhanced MR imaging. *Radiology* 1997;**203**:317–21.
19. Ash A, Shwartz M. R^2: a useful measure of model performance when predicting a dichotomous outcome. *Stat Med* 1999;**18**:375–84.

20. von Minckwitz G, Costa SD, Raab G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. *J Clin Oncol* 2001;**19**:3506–15.
21. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003;**21**:4165–74.
22. Lee AV, Cui X, Oesterreich S. Cross-talk among estrogen receptor, epidermal growth factor, and insulin-like growth factor signaling in breast cancer. *Clin Cancer Res* 2001;**12**(Suppl):4429–35.
23. Ring AE, Smith IE, Ashley S, Fulford LG, Lakhani SR. Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. *Br J Cancer* 2004;**91**:2012–7.
24. Hennessy BT, Hortobagyi GN, Rouzier R, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol* 2005;**23**:9304–11.