# Changes in Tumour Biological Markers during Primary Systemic Chemotherapy (PST)

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**Abstract.** *Background: The influence of primary systemic therapy (PST) on the expression of relevant therapeutic markers is still under investigation. Patients and Methods: Corresponding "baseline" biopsies and post-chemotherapy surgical specimens from 87 patients treated with neoadjuvant anthracycline- or taxane-based chemotherapy were analysed for the expression of the oestrogen receptor (ER), the progesterone receptor (PR), the B-cell lymphoma protein 2 (Bcl-2), the v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (Her2/neu), the tumour protein p53 and the proliferation-related Ki-67 antigen. Results: The pathological response rate was 70%. Twenty-three tumours (26%) changed hormone receptor classification after chemotherapy (7, ER; 16 PR). A significant change was also observed for Her2/neu status. Eleven tumours which were positive prior to PST down-regulated Her2/neu after chemotherapy. The median Ki-67 index decreased from 30% before to 13% after treatment (p<0.01). Minor changes were observed in the expression of Bcl-2 and p53 (9%). Only the reduction of Ki-67 was associated with pathological response to PST. Conclusion: Her2/neu status as well as ER and PR status should be re-evaluated on post-chemotherapy surgical specimens since changes can be observed.*

Primary systemic therapy (PST) is the standard treatment for locally advanced breast cancer. The major aim of systemic therapy in these patients is to facilitate breast conserving therapy and to eradicate distant micrometastatic disease. In recent years, PST has also been offered to patients with smaller tumours who were expected to receive post-operative systemic therapy (1). PST is as effective as post-operative chemotherapy in these patients, but offers the possibility of in vivo chemosensitivity testing (2-4). Moreover, based on the pathological response to chemotherapy prognostic information can be obtained. Patients with complete remission of the primary tumour have a better clinical outcome compared to those with partial remission or non-responders (5, 6).

Additionally, micrometastasis and the dissemination of tumour cells into the body's circulation which takes place at early stages of the tumour may be treated at the earliest possible moment thereby improving prognosis. Besides these clinical aspects PST provides an ideal model to evaluate the role of biological markers as predictive and prognostic factors. Many retrospective studies have identified patterns of biomarker expression before or after chemotherapy which have predictive or prognostic significance in relation to different clinical end-points.

Current clinical assessment assumes that the response of a tumour mass in total is representative of all the tumour cells and that tumours are of clonal or oligoclonal origin. However, breast cancer is characterized by its cellular heterogeneity. Therefore, PST might lead to an *in vivo* selection of a fraction of the tumour cells with different expression levels of tumour biological markers and a different phenotype compared to the pre-treatment tumour. Prior to PST tumour biological factors, such as Her2/neu, oestrogen receptor (ER) and progesterone receptor (PR) status, are routinely determined to inform post-operative, adjuvant treatment decisions regarding trastuzumab and endocrine therapy. However, if residual tumour cells do express different levels of tumour biological markers after PST these should be reassessed after PST to make sure that post-surgery treatment is tailored to the residual tumour cells.

In order to get a better insight into breast cancer response to chemotherapy this study evaluated changes in ER and PR, Her2/neu, p53, Bcl-2, and Ki-67 before and after PST.

## Patients and Methods

*Patients.* Eighty seven patients with invasive primary breast carcinoma (postchemotherapy pathologic (yp)T0–T4, ypN0–N2, grade I-III) which have underwent PST at the Department of Gynaecology and Obstetrics, University Hospital, Tuebingen,

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Table I. *Antibodies*.

| Antibodies | Antigen | Dilution | Cut-off |
|---|---|---|---|
| NCL-ER-6F111 | hER | 1:100 | >10% |
| NCL-PGR-3121 | hPR | 1:300 | >10% |
| A 04852 | Her2/neu | 1:2000 | Score 2+ / 3+ |
| DO-7[1] | p53 | 1:100 | >15% |
| clone 124[2] | bcl-2 | 1:200 | >10% |
| MIB-1, M 7240[2] | Ki-67 | 1:200 | >30% |

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Germany, from January 2002 until January 2005 were included in this study. All the patients underwent diagnostic core biopsy of the breast tumour to confirm invasive cancer before commencing treatment. All specimens were obtained after written informed consent and collected using a protocol approved by the local ethics committee (AZ 266/98).

*Chemotherapy schedules and surgery*. The patients received six cycles of either anthracycline (n=60) or taxane (n=27) based regimen administered at 21-day intervals. Surgery was performed approximately 1 month after the final cycle of chemotherapy. The patients who had no remaining invasive cancer in the breast and who were lymph node negative were considered to have a pathological complete response (CR).

*Response assessment*. The response of the tumours to the neoadjuvant chemotherapy was evaluated pathologically by classifying the regressive changes using a semiquantitative scoring system from 0 to 4 (0=no effect, 1=resorption and tumour sclerosis, 2=minimal residual invasive tumour [<0.5 cm], 3=residual non-invasive tumour only, 4=no tumour detectable) according to the tumour regression grading described by Sinn *et al*. (7). A consultant pathologist (U. Vogel) blinded to clinical outcome reviewed all paired biopsy and surgical specimens.

*Immunohistochemical technique*. The immunohistochemical (IHC) analysis was performed on both cut core biopsies and surgical resection specimens for each patient. The tissue had been fixed in 4.5% buffered formalin (pH 7.0) and embedded in paraffin. The IHC was performed on 3 to 5 μm thick sections mounted on poly-L-lysine slides using a commercially available ABC kit (Vectastain, Vector Laboratories, Burlingame, CA, USA). The primary antibodies were diluted in Tris-HCl (pH 7.5) and applied according to the manufacturer's instruction as listed in Table I. DAB (3,3' diaminobenzidine) was used as chromogen. Finally, the slides were counterstained with Mayer's hematoxylin for 10 sec and mounted for examination. For assessment of the proliferation index (Ki-67), p53 expression, ER and PR status, the percentage of cells with nuclear reactivity was recorded (8). For Bcl-2 protein expression, the percentage of cells with strong cytoplasmic or perinuclear expression was scored. For Her2/neu expression, only membranous staining was evaluated. Her2/neu expression was then scored semi-quantitatively using the 0-3+ score (0: no staining or membrane staining in <10% of tumour cells, 1+: >10% of tumour cells with weakly positive incomplete membrane staining, 2+: >10% of tumour cells with weak to moderate staining of the entire membrane, 3+: >10% of tumour cells with strong staining of the entire membrane). The cut-offs for positivity are listed in Table I.

Table II. *Basic characteristics of patients after primary systemic therapy*.

| | N (%) |
|---|---|
| Total | 87 (100) |
| Menopausal status | |
| Pre | 38 (44) |
| Post | 49 (56) |
| Tumour size | |
| ypTo | 1 (1) |
| ypT1 | 35 (41) |
| ypT2-4 | 50 (58) |
| Nodal status | |
| ypN neg | 37 (43) |
| ypN pos | 50 (57) |
| Grading | |
| I-II | 50 (58) |
| III | 33 (38) |
| missing | 4 (5) |
| Histology | |
| Ductal | 62 (71) |
| Lobular | 16 (19) |
| Others | 9 (10) |
| Primary systemic therapy | |
| Anthracycline based | 60 (69) |
| Taxane based | 27 (31) |
| Therapy response | |
| CR | 1 (1) |
| PR | 60 (69) |
| SD | 24 (28) |
| PD | 2 (2) |

ypT: post-chemotherapy pathologic T classification, ypN: post-chemotherapy pathologic N classification, CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease.

*Statistical methods*. The statistical analysis was carried out using SPSS (version 11.5; SPSS, Chigaco, IL, USA). The associations between ordinal variables were assessed using Chi-sqare analyses or the Fisher Exact Test in the case of 2 ´ 2 variables. The analyses involving Ki-67 as a continuous variable were investigated using ANOVA.

## Results

*Clinical characteristics*. The clinical data are presented in Table II. After PST 41% of the patients had ypT1 and 58% had ypT2-T4 tumours with grade I-II in 58% and III in 38% of the cases. Positive lymph nodes were seen in 57% of the patients. The predominant tumour type was invasive ductal carcinoma (71%) followed by lobular carcinoma in 19% of the cases.

*Response to treatment*. Out of the 87 patients, treated with neoadjuvant chemotherapy, one patient showed complete remission (CR). Partial remission (PR) was seen in 60 patients and stable disease (SD) or progression of disease (PD) was observed in 24 patients and five patients, respectively. The pathological response rate was 70% (Table II).

Table III. *Tumour biological factors before and after primary systemic therapy.*

| Marker | N | Neg–neg | Pos–pos | Neg–pos | Pos–neg | Change |
|---|---|---|---|---|---|---|
| ER | 87 | 24 (28%) | 56 (64%) | 3 (3%) | 4 (5%) | 7 (8%) |
| PR | 87 | 36 (41%) | 35 (40%) | 3 (3%) | 13 (15%) | 16 (18%) |
| Her2/neu | 86 | 46 (53%) | 27 (31%) | 2 (2%) | 11 (13%) | 13 (15%) |
| p53 | 62 | 38 (61%) | 16 (26%) | - | 8 (13%) | 8 (13%) |
| Ki-67 | 63 | 25 (40%) | 14 (22%) | 2 (3%) | 22 (35%) | 24 (38%) |
| Bcl-2 | 62 | 12 (19%) | 42 (68%) | 2 (3%) | 6 (10%) | 8 (13%) |

Table IV. *Treatment related changes of ER and PR.*

| | PR status | | | | |
|---|---|---|---|---|---|
| | neg → neg | neg → pos | pos → neg | pos → pos | Total |
| ER status | | | | | |
| neg → neg | 22 | 0 | 2 | 0 | 24 |
| neg → pos | 1 | 1 | 0 | 1 | 3 |
| pos → neg | 1 | 0 | 3 | 0 | 4 |
| pos → pos | 12 | 2 | 8 | 34 | 56 |
| Total | 36 | 3 | 13 | 35 | 87 |

*Expression of biological markers.* The expression of the different tumour markers determined in the diagnostic "baseline" biopsies and post-chemotherapy surgical specimens and the changes of tumour biological factor expression during treatment are shown in Table III.

The expression of ER was assessed in all 87 pre- and post-chemotherapy sample pairs and remained the same in 80 of them. Three initially ER negative tumours were ER positive and four initially ER positive tumours were negative after chemotherapy. The difference in ER expression level before and after chemotherapy exposure was not statistically significant. The expression of PR was also determined in all 87 pre- and post-chemotherapy sample pairs and no change in expression was observed in 71. A switch from PR negative before to PR positive post-chemotherapy was detected in 3% and from PR positive before to negative after chemotherapy in 15%.

Her2/neu expression remained unchanged in 73 out of 86 tested pre- and post-chemotherapy sample pairs. In two patients, Her2/neu expression switched from negative before to positive after PST while in 11 cases it changed from positive to negative.

Expression of p53 and bcl-2 remained unchanged in 87% of the 62 pre- and post-chemotherapy sample pairs which could be determined. The difference in p53 or bcl-2 expression level before and after PST was not statistically significant. Ki-67 expression remained unchanged in 62% of the 63 cases determined. In 3% the expression switched from negative to positive while in 35% the Ki-67 count was positive before treatment and negative after PST. The mean proliferation fraction was 30% before PST and 13% after chemotherapy ($p<0.001$, two-sided *t*-test for paired samples). Only the reduction of Ki-67 was associated with pathological response to PST.

*Correlation of different tumour biological markers.* Significant correlations of the expression were obtained for ER and PR ($p<0.01$, Table IV) and for PR and Bcl-2 ($p<0.01$, data not shown). For ER and PR, 19 tumours changed the expression of either or both receptors (22%). Ten of them did not change the expression of ER, but switched from PR positive to PR negative after PST (53%). Additionally, three tumours regulated both, ER and PR, down after PST (16%).

## Discussion

Significant effects on the expression of tumour biological markers by primary chemotherapy are controversely discussed with some groups reporting no changes (9-14) and others observing changes (15-20, Table V) of expression. Rody *et al*. (15) obtained a switch in expression for ER, PR, or Her2/neu from positive to negative in 45.7% of cases and vice versa in 22.7% following neoadjuvant chemotherapy. In a study performed by Piper *et al*. (16) of those patients who did not achieve a pCR, a change in tumor markers was seen in 25.7% of patients. ER changed in 33% and PR in 42%. Her2 changed in 25% of the patients. Burcombe *et al*. (17) report that 9% of the tumours changed hormone receptor classification after neoadjuvant chemotherapy (3% ER, 6% PR); HER-2 staining changed in nine cases. Median Ki-67 index was 24.9% before and 18.1% after treatment. In another study a significant decrease in the ER levels by 24% in patients responding to anthracycline-based PST was detected (18). Further, a significant change in hormonal receptor content after pre-operative chemotherapy was observed in a total of 33% of patients (19). ER changed in 17%, PR in 22%, and both ER and PR in 6%. However, ER and PR status did not appear to predict or correlate with response to chemotherapy (19). Finally, a significant down-regulation of ER (14%) and PR (52%) was also identified using hormone receptor IHC in breast cancer patients receiving different regimens of PST (20). Seven (50%) of these patients were pre-menopausal suggesting that PST may have exerted an endocrine effect by rendering women post-menopausal after chemotherapy. Their observations might also explain

Table V. *Overview of published response rates and changes of tumour biological factors during treatment.*

| Reference | Year | No. of patients | Treatment | Change of tumour biological marker | | | |
|---|---|---|---|---|---|---|---|
| | | | | ER | PR | Her2 | Ki-67 |
| (15) | 2006 | 70 | AT | ← 45.7% [a,d], 22.7% [a,e] → | | | n.d. |
| (16) | 2004 | 43 | A, AT | ← 25.7% [a] → | | | n.d. |
| | | | | 33% | 42% | 25% | |
| (17) | 2005 | 118 | A, MMM | 3% | 6% | 8% | 24.9% → 18.1% |
| (18) | 1997 | 29 | A, CMF | 24% c, s | n.c. | n.d. | 15% → 11% * |
| (19) | 1996 | 21 | A, CMF | ← 33% a, 6% [b] → | n.d. | n.d. | |
| | | | | 17% | 22% | | |
| (20) | 2003 | 191 | A, CMF, T | 14% [d] | 52% [d] | n.d. | n.d. |

A: anthracycline-containing regimen, T: taxane-containing regimen, MMM: methotrexate/mitoxantrone/mitomycin, CMF: cyclophosphamide/methotrexate/5-fluorouracil, *=not significant, s=significant. a) change of at least one marker, b) change of both markers, c) change of mean in responders, d) change from positive to negative; e) change from negative to positive. n.c.= no change, n.d.=not determined.

our result that most tumours down-regulating PR were ER positive (n=8) as this might indicate a change in ER signaling capacity. An attractive hypothesis to explain the progression to steroid independence is that the tumour acquires the ability to constitutively express autocrine growth factors. In MCF-7 cells it has been observed that overexpression of fibroblast growth factor (FGF) induced an oestrogen-independent phenotype, which acted downstream of the ER as the ER level was not changed in these cells (21). The predictive value of PR has long been attributed to the dependence of PR expression on ER activity, with the absence of PR reflecting a nonfunctional ER. Two neoadjuvant studies confirmed the observation that PR negative tumours respond less well to hormonal therapy than PR positive tumours (22, 23). It might therefore well be that neoadjuvant chemotherapy is selecting for residual PR negative tumour cells or tumour cells that are able to alter their PR expression resulting in recurrences less susceptible to hormonal therapy. These data along with our results indicate that post-operative marker studies should be performed given the possibility of a change in status.

A majority of studies have confirmed that rapidly proliferating tumours confer a poor prognosis (24-33). A reduction in Ki-67 index has been demonstrated after neoadjuvant chemotherapy (10, 17, 34), tamoxifen therapy (35), and chemoendocrine therapy (36, 37). Our observation that the median Ki-67 index dropped from 30% to 13% post-PST was in line with them and indicated that chemotherapy was exerting an anti-proliferative effect on the tumours. This suggests that probably a proliferating state renders tumour cells more sensitive to chemotherapy since structural damage during DNA synthesis induced by anthracycline exposure decreases the viability of newly formed cancer cells (10, 38-44).

The reduction of Ki-67 labelling in residual tissue at the end of chemotherapy, raises the question of whether the decrease in proliferation resulted from down-regulation in the entire cell population by a triggered 'switching off' of proliferative regulators, or reflected selection of residual, less proliferative cells that were intrinsically less sensitive to chemotherapy and were preserved throughout treatment.

The difference in p53 expression level before and after chemotherapy exposure was not statistically significant in our study. Similarly, several neoadjuvant studies have failed to detect a predictive value of p53 staining with regards to chemoresponsiveness in breast carcinomas (45-48). However, evidence from *in vitro* (49) and animal studies (50) has shown that defective p53 was associated with resistance to chemotherapy. Furthermore, loss of p53 function correlated with multidrug resistance in many tumour types and specific p53 mutations have been associated with resistance to doxorubicin in the neoadjuvant setting (51, 52).

The situation of Bcl-2 expression in breast cancer is not clear-cut with some studies indicating that Bcl-2 has no predictive value in terms of chemoresponse (18, 41, 53, 54). These data support our results that the difference in Bcl-2 expression level before and after chemotherapy exposure was not statistically significant. In contrast, in a very small series of women with advanced breast cancer, Bcl-2 negativity was associated with an increased response rate to neoadjuvant chemotherapy (47). Interestingly, in our study Bcl-2 expression correlated with the expression of PR as has been observed by others before in breast cancer (55) and endometrial cancer (56).

The transmembrane receptor Her2/neu is overexpressed in about 25% of breast tumours (57) and is associated with poor outcome (58), and relative sensitivity to anthracycline

regimens (59, 60). In our study 13% of the tumours switched from Her2/neu positive to Her2/neu negative after PST. However, it could not be distinguished if the receptor was actively down-regulated in theses cases or if neoadjuvant treatment was selecting for Her2/neu negative tumour cells. Taucher *et al*. analyzing an anthracycline/taxane-based neoadjuvant therapy regime found no significant change of Her2/neu expression (61). Thus, at present, the data in neoadjuvant studies are conflicting with respect to Her2/neu status and response to anthracyclines, but based on our results we recommend that the Her2/neu score is re-evaluated in post-treatment tissue.

A possible reason for the observed status variation may be reflected by either sampling error within heterogeneous tumours or the immunostaining of core biopsies. Our sample cohort did not include non-neoadjuvant therapy control patients for comparison. It has been reported that ER/PR status changed in 5-6% of neoadjuvant chemotherapy and control groups due to tissue sampling (16, 62). If 5-6% is deducted from the 26% total ER/PR changes, approximately 20% of the hormone receptor changes would still have been caused by neoadjuvant treatment. Also, in a previously reported series of 236 patients treated without intervening chemotherapy the hormone receptor status was highly representative of the entire resected tumour (20). This result suggests that sampling error did not account for the observed hormone receptor "down-regulation" seen in some cases.

A second cause of variation might be technical as a recent study has shown a discordance rate in hormone receptor (HR) status of 9% between core biopsy and surgical specimens due to fixation or technical artefacts of IHC (63, 64). However, such discordance of HR status was very low (3%) in a previously reported control group (65). Thus although some of the discordance observed in our series might have been caused by technical caveats the published data suggest that such differences are rare and have minor clinical significance.

We therefore conclude that the changes in tumour marker expression observed in our study were changes induced by the treatment itself. Patients treated with adjuvant hormonal therapy are traditionally selected by an assessment of their HR status since HR-positive status predicts response to adjuvant hormonal therapy. Therefore, if PST changes the phenotype of the residual tumour cells, post-operative, adjuvant treatment decisions regarding *e.g.* trastuzumab and endocrine therapy might be optimized by re-evaluating the expression level of Her2/neu and ER on post-surgical tumour tissues. This view is supported by the observation that residual disease after PST, rather than parameters evaluated on the initial tumour biopsy, should be considered for patient prognosis (66). Survival after PST was related to the HR status of

the residual disease with a high discordance in the HR status between the initial biopsy and the remaining tumour at surgery.

## Conclusion

Her2/neu status as well as ER and PR status should be re-evaluated on post-chemotherapy surgical specimens since changes can be observed. The clinical relevance of these changes to adjuvant endocrine therapy or trastuzumab requires further long term follow-up and until such data becomes available, caution should be exercised when basing adjuvant therapy regimens on pre-operative tumour marker studies alone.

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