Original Scientific Paper

Eur Surg (2004) 36/1: 41–45

EUROPEAN SURGERY
ACA Acta Chirurgica Austriaca
Printed in Austria

The impact of progesterone receptor in prediction of complete pathological response to preoperative chemotherapy in primary breast cancer patients

S. Taucher[1], **M. Rudas**[2], **M. Gnant**[1], **P. Dubsky**[1], **E. Sporn**[1], **S. Roka**[1], **T. Bachleitner**[1], **F. Fitzal**[1], **D. Kandioler**[1], **C. Wenzel**[3], **G. Steger**[3], **W. Draxler**[1], **M. Mittlböck**[4] and **R. Jakesz**[1]

[1]University of Vienna, Department of Surgery, [2]Department of Pathology, [3]First Medical Department and [4]Department of Medical Computer Sciences, Division of General Surgery, Vienna, Austria

(Received July 28, 2003; accepted and revised September 02, 2003)

Die Wertigkeit des Progesteronrezeptors als prädiktiver Marker einer kompletten pathologischen Remission nach präoperativer Chemotherapie bei Patientinnen mit primärem Mammakarzinom

Zusammenfassung. *Grundlagen:* Der Vorteil einer präoperativen Chemotherapie bei Patientinnen mit Mammakarzinom ist nach Erreichen einer kompletten pathologischen Remission (pCR) am grössten. Das Ziel dieser Analyse war die Wertigkeit des Progesteronrezeptors als prädiktiver Marker für das Erreichen einer pCR nach präoperativer Chemotherapie bei Patientinnen mit Mammakarzinom zu bestimmen.

Methodik: 213 Patientinnen mit primärem Mammakarzinom erhielten eine präoperative Chemotherapie. Wir haben den prädiktiven Wert von Östrogen- (ER) und Progesteronrezeptor (PR) im Biopsiematerial auf das Ansprechen nach präoperativer Chemotherapie untersucht. Der Zusammenhang zwischen Hormonrezeptoren und pCR wurde mit dem Fisher's exact und mit dem Chi-quadrat Test bestimmt.

Ergebnisse: Eine pCR haben 23 Patientinnen erreicht (10.8 %), sie alle waren PR-negativ. Ein negativer ER und PR waren signifikant häufig mit einer pCR assoziiert ($p = 0.00028$ und $p = 0.0003$).

Schlussfolgerungen: Unsere Ergebnisse zeigen, dass ein negativer ER und PR-status wichtige prädiktive Marker für das Erreichen einer pCR nach präoperativer Chemotherapie darstellen. Bei PR-positiven Patientinnen mit Mammakarzinom zeigte sich keine einzige pCR, daher ist eine präoperative Chemotherapie bei PR-positiven Patientinnen nicht zu empfehlen.

Correspondence: S. Taucher, M. D., Division of General Surgery, Department of Surgery, University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria.
Fax: ++43/1/533 47 67
E-mail: susanne.taucher@univie.ac.at

Schlüsselwörter: Mammakarzinom, Nadelbiopsie, Östrogenrezeptor, Progesteronrezeptor, präoperative Chemotherapie.

Summary. *Background:* The benefit of preoperative chemotherapy on outcome in breast cancer has been shown to be highest in patients with complete pathological response (pCR). The objective of this analysis was to determine the predictive value of progesterone receptor status on pCR rate in primary breast cancer patients receiving preoperative chemotherapy.

Methods: Preoperative chemotherapy was administered to 213 patients with primary breast cancer. We assessed the predictive impact of estrogen (ER) and progesterone receptor (PR) in biopsy tissue on response to preoperative chemotherapy. The association of steroid receptor status and pCR was tested by Fisher's exact and Chi quadrate test.

Results: pCR was achieved in 23 patients (10.8 %). All patients experiencing pCR were PR negative (100 %). ER and PR negativity was significantly associated with pCR, $p = 0.00028$ and $p = 0.0003$, respectively.

Conclusions: We conclude from our results that ER and PR negativity represent valuable markers predicting pCR after primary chemotherapy. In PR positive breast cancer patients no single case of pCR was observed, therefore we may recommend no preoperative chemotherapy in PR positive patients.

Key words: Breast cancer, core needle biopsy, estrogen receptor, progesterone receptor, preoperative chemotherapy.

Introduction

The administration of chemotherapy prior to surgery, called primary or neoadjuvant chemotherapy, offers potential advantages to patients with primary breast cancer. Large clinical trials of neoadjuvant chemotherapy have

established that pathological complete remission (pCR) represents an independent predictor of improved disease-free survival [12]. However, prediction of response to primary chemotherapy is a matter of continuing debate.

Estrogen (ER) and progesterone receptor (PR) determinations are established procedures in the routine management of patients with breast cancer, chiefly as predictive factors for response to adjuvant and palliative endocrine therapy [2, 6, 13]. In addition, the selection of preoperative treatment modalities needs to be directed by molecular markers like steroid hormone receptor status. Chang and others [1, 5, 21] have shown that pretreatment ER and PR significantly predict the response to preoperative administration of tamoxifen.

The selection of preoperative chemotherapy is currently based on such clinical factors as tumor size more so than on molecular markers. Preoperative chemotherapy has shown to increase the percentage of breast conservation, but does not positively correlate with overall survival [12, 24]. In addition to the absence of c-erbB-2, the lack of ER has recently been demonstrated to significantly predict subsequent good clinical response. Lack of ER expression additionally predicted increased risk of death [5]. Little is known about the role of PR status on response in patients receiving preoperative chemotherapy.

The objective of this analysis was to determine the predictive impact of PR status on response rate, namely pCR to primary chemotherapy.

Material and methods

We evaluated 213 patients with palpable primary breast cancer in an attempt to assess the predictive impact of ER and PR status on pCR to neoadjuvant chemotherapy. Patient characteristics are summarized in table 1. Tumor tissue was obtained pretherapeutically by core needle biopsy (2–5 cores, mean 3 cores) and ER and PR status was assessed in biopsy tissue and in the surgically removed specimen subsequent to chemotherapy (supervised by a single pathologist, M. R.). Core needle biopsy was performed under local anesthesia using a 15-gauge needle (ASAP Detachable™ Biopsy System) on an outpatient basis. Core needle biopsy specimen and surgically removed specimen were both fixed in neutral-buffered formalin (4.5 %) for 24 hours and embedded in paraffin. Paraffin-embedded tissue sections of 3 μm thickness were used for staining.

ER and PR determination were performed in immunohistochemistry as described previously [22]. In brief, those tissue sections with a cut-off of less than 10 % stained cells and at least weak intensity of staining were recorded as hormone receptor-negative, those with more than 10 % stained cells were considered as receptor-positive and classified as follows: weakly positive, 10–50 % stained tumor tissue with weak or moderate intensity; medium positive, 51–80 %, weak or moderate intensity; strongly positive, those with more than 80 % of moderate or strong intense staining.

All patients required downstaging by preoperative chemotherapy to facilitate breast-conserving surgery. We administered three different chemotherapeutical schedules preoperatively to our patients. Cyclophosphamide, methotrexat and fluorouracil (CMF; 600/40/600 mg/m^2) was used primarily being a part of a clinical study, Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 7 [15]. 62 patients (29.1 %) received 3 courses of CMF every 4 weeks preoperatively.

Table 1. Patients' characteristics

Characteristics	n = 213	%
Age, years		
median	51	
range	33–75	
premenopausal	84	39.4
postmenopausal	129	60.6
Clinical tumor size		
T1	6	2.8
T2	125	58.7
T3	46	21.6
T4	36	16.9
Preoperative therapy		
CMF	62	29.1
FEC	68	31.9
Taxane-containing regimen	83	39.0
Response to chemotherapy		
pCR	23	10.8
pPR	113	53.0
pNC	73	34.3
pPD	4	1.9
Surgical procedure		
breast conservation	144	67.6
mastectomy	69	32.4
Pathological tumor stage		
pT0 / DCIS	23 / 10	10.8 / 4.7
pT1	95	44.6
pT2	57	26.8
pT3	20	9.4
pT4	18	8.4
Pathological nodal stage		
pN0	94	44.1
pN1	116	54.5
pNx	3	1.4
Histological type		
ductal cancer	159	74.6
lobular cancer	29	13.6
others	25	11.8
Grading		
G1, G2, Gx	109	51.2
G3	81	38.0
unknown	23	10.8

CMF = cyclophosphamide, methothrexate, fluorouracil, FEC = fluorouracil, epirubicin, cyclophosphamide

Since 1996, when increasing evidence was presented that anthracycline-containing chemotherapeutic regimen showed higher response rates, this kind of chemotherapy has mainly been employed. An anthracycline-containing regimen (fluorouracil, epirubicin and cyclophosphamide, FEC; 600/60/600 mg/m^2) was subsequently introduced for preoperative treatment. Nearly one third of all patients (67 patients, 31.5 %) received 3 to 6 cycles of FEC every three weeks prior to surgery.

Several patients (84 patients, 39.4 %) received the combination of anthracycline and taxotere. We administered epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 (ED) intravenously (i.v.) every three weeks, supported by G-CSF (day 3 to 10). In 9 patients, preoperative chemotherapy with ED was followed by second-line therapy either with CMF or FEC due to minimal response to ED. One to six cycles (mean 4) of ED were administered preoperatively until best possible response was achieved.

Response to chemotherapy was assessed according to the International Union Against Cancer (UICC) guidelines [14]. Complete pathological response (pCR) was defined as complete disappearance of invasive tumor cells, irrespective of possibly residual, yet exclusively intraductal component. Reduction of tumor size of at least 50 % was defined as partial remission, reduction of tumor size of less than 50 % was considered as stable disease, any increase in tumor size in the course of preoperative therapy was determined as progressive disease.

Breast-conserving surgery was performed in 144 patients (67.6 %) receiving preoperative cytotoxic treatment. All women treated with breast conserving surgery received postoperative irradiation. In patients undergoing modified radical mastectomy, postoperative radiotherapy was left to the discretion of the responsible physician based on consultation within the interdisciplinary team.

Statistical analysis: The association between ER and PR and response rate was calculated by Fisher's exact test and Chi quadrate test (χ^2).

Results

The overall response rate was 63.4 %, 23 patients (10.8 %) responded excellently and achieved pCR with no residual invasive cancer in the surgical specimen. Among 23 patients having pCR, in 5 patients the residual tumor tissue did show ductal in-situ cancer. Tumor shrinkage of more than 50 % was achieved in 113 patients (53 %). The primary tumor size was reduced by preoperative treatment less than 50 % in 73 patients (34.3 %).Only 4 patients (1.9 %) did not respond to preoperative chemotherapy and developed progressive disease.

Comparisons of response outcomes among groups with different steroid receptor status tested by Fisher's exact test yielded significantly better response in ER and PR negative patients. Details are given in table 2. In those patients achieving pCR, the primary tumor tissue was always PR negative prior to chemotherapy. In 20 patients out of 23, the primary tumor tissue was ER negative, in the remaining 3 patients responding excellently to preoperative chemotherapy ER was weak positive (2 patients) and medium positive (1 patient).

The association of PR status and response tested with χ^2 test confirmed a significant likelihood of PR negative patients to respond excellently and achieved pCR after primary chemotherapy (p = 0.0015). Out of 153 patients with PR negative breast cancer, 23 (15 %) achieved pCR, whereas out of 60 patients with PR positive breast cancer, no single patient (0 %) responded excellently (no pCR) to preoperative chemotherapy. The sensitivity of PR status to predict pCR in patients with PR negative tumor assessed in core needle biopsy specimen was 100 % (95 % CI: 87.8–100 %). Whereas the sensitivity of PR positive patients to predict any response other than pCR was again 100 % (95 % CI: 95.1–100 %).

Table 2. ER and PR status in patients receiving preoperative chemotherapy. Comparison between pCR and incomplete response (= partial remission, stable and progressive disease), tested by Fisher's exact test

	pCR, n = 23		incomplete response, n = 190		
	No.	%	No.	%	*p*
ER negative	20	18.1	90	81.9	0.0002
ER positive	3	2.9	100	97.1	
PR negative	23	15.0	130	85.0	0.0003
PR positive	0	0	60	100	

The association of ER status and response tested by χ^2 test did show similar results. In ER negative patients the likelihood of achieving pCR after preoperative

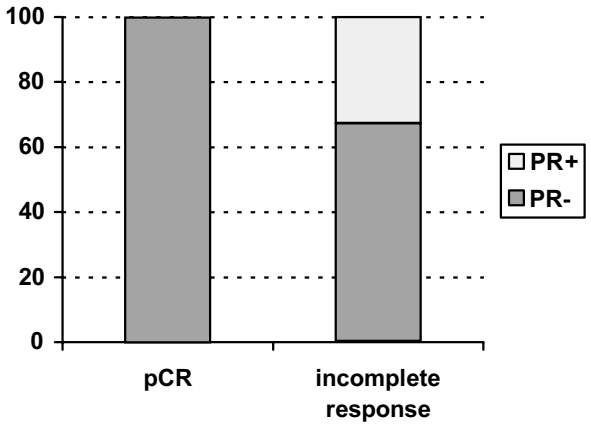

Fig. 1. Association of PR status and response (1 = 100 %)

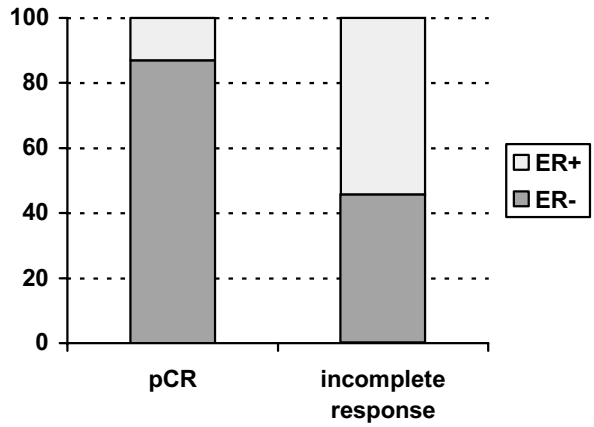

Fig. 2. Association of ER status and response (1 = 100 %)

chemotherapy was significantly better ($p = 0.0003$). Among 110 patients with ER negative breast cancer, 20 patients (18.2 %) experienced pCR, whereas among 103 patients with ER positive breast cancer only 3 patients (2.9 %) achieved pCR. The sensitivity of ER status to predict pCR in patients with ER negative tumor assessed in core needle biopsy specimen was 87 % (95 % CI: 66.4–97.2 %). Whereas the sensitivity of ER positive patients to predict any response other than pCR was 97.1 % (95 % CI: 91.7–99.4 %).

We investigated the association between other biological markers and response to preoperative chemotherapy. No significant correlation between pCR and HER2/neu, p53, Mib or grading was found.

Discussion

The aim of this study was to provide a better insight into the relation between steroid receptor status and response to preoperative chemotherapy.

Our results indicate a significant association of ER, PR and response to preoperative treatment. Steroid hormone receptors have proven to be the most important predictive markers for selection of systemic treatment, in particular of postoperative endocrine treatment [10, 16]. However, the predictive role of steroid receptor status for response to chemotherapy is still an open question. Our data indicate that steroid receptor status is a marker of chemo sensitivity in breast cancer. Apparently, PR negative breast carcinomas are more sensitive to primary chemotherapy. These results are in line with reports by others [17, 19], showing the prediction of response to chemotherapy by ER negativity. However, we could demonstrate the even more important impact of PR status.

We could clearly show that PR positive patients are never complete responders after neoadjuvant chemotherapy. One of the most important benefits of preoperative chemotherapy is not so much the early identification of patients who will have an excellent response to chemotherapy but rather the identification of patients who will have only a minimal response. These patients must be immediately identified to spare them additional ineffective and toxic treatment. In this regard, it is of particular interest that PR positive patients never achieved pCR.

There are very few reports that have addressed clinicopathologic factors associated with the complete histologic resolution of invasive tumor in the breast [7, 8, 11, 17]. More than twenty years ago, Lippman et al. [18] reported on the relationship between ER and response to chemotherapy in metastatic breast cancer patients. Lippman et al found statistically increased objective response rates to cytotoxic therapy in patients with low or absent ER values, compared with highly ER positive patients. In the neoadjuvant setting, higher response rates in ER negative patients were reported more recently [4, 20]. In the adjuvant setting, noticeable is the latest overview of randomized trials of polychemotherapy for breast cancer in which the proportional reduction in recurrence was found to be significantly greater for women of all ages with ER negative tumors, compared with women with ER positive tumors [9]. Our results are consistent with data derived in the last 25 years in the metastatic, neoadjuvant and in the adjuvant setting. However, our results point out the significant importance of PR status with respect to cytotoxic treatment in the preoperative management of breast cancer patients. PR status might provide additional information to predict more accurately which patients will respond to preoperative treatment, possibly because the presence of PR should serve as an indicator of a functionally intact estrogen response pathway. The predictive value of PR status in the adjuvant setting of endocrine treatment has been shown recently [3].

Until now, the only demonstrated benefit from preoperative chemotherapy is the improvement in surgical breast conservation [24], whereas no definite advantage concerning survival has yet been shown [12]. However, those patients achieving pCR after primary chemotherapy have been shown to benefit regarding overall survival and disease-free survival as well [24]. Our data indicate a pCR rate of 10.8 % with different cytotoxic regimens. The patient groups were well-balanced. No statistically significant difference in response rates was found between the different chemotherapy schedules. Taking these aspects into consideration, we could demonstrate that the association between steroid receptor status and response was independent of the cytotoxic regimen that had been used.

The assessment of steroid receptor status in core needle biopsy has been proven to be a valid tool [23]. Upcoming therapeutical options including preoperative hormonal treatment can be based on the results of ER and PR evaluation in core needle biopsy. However, preoperative therapy may modulate the ER and PR content of the tumor. In our study, paying attention to the biological characteristics of patients achieving pCR, the question of steroid receptor modulation by preoperative therapy could not be answered, because no vital tumor tissue was available after therapy.

In conclusion, the results of this study suggest that steroid receptor status should be considered as a predictive marker of pCR after preoperative chemotherapy. In PR positive patients, no single case of pCR was observed, and therefore we can recommend the avoidance preoperative chemotherapy in patients with positive PR status in order to spare them unnecessary side effects. However, further trials are to be designed to clarify the obviously important interaction between receptor biology and cytotoxic chemotherapy.

References

1. Allegra JC, Lippman ME, Thompson EB, Simon R, Barlock A, Green L, Huff KK, Do HM, Aitken SC, Warren R (1980) Estrogen receptor status: an important variable in predicting response to endocrine therapy in metastatic breast cancer. Eur J Cancer 16: 323–331
2. Allred DC, Harvey JM, Berardo M, Clark GM (1998) Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 11: 155–168
3. Bardou V-J, Arpino G, Elledge RM, Osborne CK, Clark GM (2003) Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J Clin Oncol 21: 1973–1979

4. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, Bartoli C, Coopmans de Yoldi G, Zucali R, Rilke F et al. (1990) Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 82: 1539–1545
5. Chang J, Powles TJ, Allred DC, Ashley SE, Clark GM, Makris A, Assersohn L, Gregory RK, Osborne CK, Dowsett M (1999) Biologic markers as predictors of clinical outcome from systemic therapy for primary operable breast cancer. J Clin Oncol 17: 3058–3063
6. Clark GM (1996) Prognostic and predictive factors. In: Harris JR, Lippman ME, Morrow M and Hellman S (eds) Diseases of the breast. Lippincott-Raven, Philadelphia, pp 461–485
7. Cleator S, Parton M, Dowsett M (2002) The biology of neoadjuvant chemotherapy for breast cancer. Endocr Relat Cancer 9: 183–195
8. Colleoni M, Orvieto E, Nole F, Orlando L, Minchella I, Viale G, Peruzzotti G, Robertson C, Noberasco C (1999) Prediction of response to primary chemotherapy for operable breast cancer. Eur J Cancer 35: 574–579
9. Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 352: 930–942
10. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 351: 1451–1467
11. Faneyte IF, Schrama JG, Peterse JL, Remijnse PL, Rodenhuis S, van de Vijver MJ (2003) Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. Br J Cancer 88: 406–412
12. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher E, Wickerham D, Begovic M, DeCillis A, Robidoux A, Margolese R, Cruz A, Jr, Hoehn J, Lees A, Dimitrov N, Bear H (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 16: 2672–2685
13. Harvey JM, Clark GM, Osborne CK, Allred DC (1999) Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 17: 1474–1481
14. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD (1977) Assessment of response to therapy in advanced breast cancer: a project of the Programme on Clinical Oncology of the International Union Against Cancer, Geneva, Switzerland. Cancer 39: 1289–1294
15. Jakesz R (2001) Comparison of pre- vs. postoperative chemotherapy in breast cancer patients: four-year results of Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 7. American Society of Clinical Oncology 20: 32a
16. Jakesz R, Hausmaninger H, Samonigg H (2002) Chemotherapy versus hormonal adjuvant treatment in premenopausal patients with breast cancer. Eur J Cancer 38: 327–332
17. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN, Singletary SE (1999) Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 17: 460–469
18. Lippman ME, Allegra JC (1980) Quantitative estrogen receptor analyses: the response to endocrine and cytotoxic chemotherapy in human breast cancer and the disease-free interval. Cancer 46: 2829–2834
19. MacGrogan G, Mauriac L, Durand M, Bonichon F, Trojani M, de Mascarel I, Coindre JM (1996) Primary chemotherapy in breast invasive carcinoma: predictive value of the immunohistochemical detection of hormonal receptors, p53, c-erbB-2, MiB1, pS2 and GST pi. Br J Cancer 74: 1458–1465
20. Mauriac L, Durand M, Avril A, Dilhuydy JM (1991) Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Results of a randomized trial in a single centre. Ann Oncol 2: 347–354
21. Mouridsen H, Palshof T, Patterson J, Battersby L (1978) Tamoxifen in advanced breast cancer. Cancer Treat Rev 5: 131–141
22. Reiner A, Neumeister B, Spona J, Reiner G, Schemper M, Jakesz R (1990) Immunocytochemical localization of estrogen and progesterone receptor and prognosis in human primary breast cancer. Cancer Res 50: 7057–7061
23. Taucher S, Rudas M, Gnant M, Thomanek K, Dubsky P, Roka S, Bachleitner T, Kandioler D, Wenzel C, Steger G, Mittlbock M, Jakesz R (2003) Sequential steroid hormone receptor measurements in primary breast cancer with and without intervening primary chemotherapy. Endocr Relat Cancer 10: 91–98
24. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B (2001) 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 30: 96–102