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Chemotherapy Is More Effective in Patients with Breast Cancer Not Expressing Steroid Hormone Receptors: A Study of Preoperative Treatment

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ABSTRACT

Purpose: **The purpose of this research was to identify factors predicting response to preoperative chemotherapy.**

Experimental Design: **In a large volume laboratory using standard immunohistochemical methods, we reviewed the pretreatment biopsies and histologic specimens at final surgery of 399 patients with large or locally advanced breast cancer (cT2-T4, N0–2, M0) who were treated with preoperative chemotherapy. The incidence of pathological complete remission and the incidence of node-negative status at final surgery were assessed with respect to initial pathological and clinical findings. Menopausal status, estrogen receptor status, progesterone receptor status [absent (0% of the cells positive) *versus* expressed], clinical tumor size, histologic grade, Ki-67, Her-2/*neu* expression, and type and route of chemotherapy were considered.**

Results: **High rates of pathological complete remission were associated with absence of estrogen receptor and progesterone receptor expression ($P < 0.0001$), and grade 3 ($P = 0.001$). Significant predictors of node-negative status at surgery were absence of estrogen receptor and progesterone receptor expression ($P < 0.0001$), clinical tumor size <5 cm ($P < 0.001$), and use of infusional regimens ($P = 0.003$). The chance of obtaining pathological complete remission or node-negative status for patients with endocrine nonresponsive tumors compared with those having some estrogen receptor or progesterone receptor expression was 4.22 (95% confidence interval, 2.20–8.09, 33.3% *versus* 7.5%) and 3.47 (95% confidence interval, 2.09–5.76, 42.9% *versus* 21.7%), respectively. Despite the significantly higher incidence of pathological complete remission and node-negative status achieved by preoperative chemotherapy for patients with estrogen receptor and progesterone receptor absent disease, the disease-free survival was significantly worse for this cohort compared with the low/positive expression cohort (4-year disease-free survival %: 41% *versus* 74%; hazard ratio 3.22; 95% confidence interval, 2.28–4.54; $P < 0.0001$).**

Conclusions: **Response to preoperative chemotherapy is significantly higher for patients with endocrine nonresponsive tumors. New chemotherapy regimens or combinations should be explored in this cohort of patients with poor outcome. For patients with endocrine responsive disease, the role of preoperative endocrine therapies should be studied.**

INTRODUCTION

Experimental data support the hypothesis that chemotherapy given before surgery for breast cancer may improve patient outcome (1–4), yet the most effective timing and sequencing for systemic chemotherapy in operable breast cancer is still unclear. Outside clinical trials, such treatment is indicated only for patients with locally advanced disease or those in whom a reduction of primary tumor size may allow breast conservation. In fact, the only demonstrated benefit of preoperative chemotherapy in terms of treatment effects is the achievement of tumor shrinkage sufficient to allow breast saving surgery in some of the patients (*i.e.*, dependent also on breast size, tumor size, and conditions allowing radiation therapy to the conserved breast). Several randomized trials comparing primary chemotherapy with traditional adjuvant treatment have been published, and no clear advantage in disease-free survival or overall survival was observed (5–12). Despite these unsatisfactory results, not a single trial led to an observation of a trend indicating that primary chemotherapy was detrimental. Surgical complications were not more prevalent, and the positive aspect was that more patients could be offered breast-conserving surgery after primary systemic treatment.

Preoperative chemotherapy might be advantageous for patients with breast cancer in several ways in addition to allowing breast conservation surgery in some of the patients. The response to the primary treatment may be used as a prognostic marker, because it was demonstrated to be associated with a longer disease-free survival compared with no response (9). Not only the response but also the type and degree of response

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(pathological complete remission) predict overall outcome in terms of disease-free survival (9). Finally, observed patterns of change for various biological features after exposure to primary treatment might also serve as a surrogate for qualitative and quantitative prediction of response.

Several strategies can be considered to improve results of preoperative chemotherapy. On one hand, the introduction of new drugs in preoperative chemotherapy regimens might provide some benefit as indicated recently in randomized trials (13, 14). A second useful strategy to improve knowledge about treatment effects is the early identification of features, which are associated with response or resistance to primary therapy. Identifying these features is a crucial step in the development of the most effective multimodal approaches, using a sequence of local and systemic treatments and identifying cohorts of patients most likely to benefit from preoperative chemotherapy.

To seek information on the predictive value of biological and clinical features we evaluated the course of disease in 399 patients with large operable primary breast cancer who had preoperative diagnosis and surgery performed at the European Institute of Oncology.

PATIENTS AND METHODS

Patients. Prospectively collected data from 399 consecutive patients with clinical stage T2-T4d, N0–2 treated with preoperative chemotherapy from 1994 through 2002 were analyzed. Eligibility criteria for preoperative chemotherapy included no previous chemotherapy/hormonotherapy, performance status 0–2 (Eastern Cooperative Oncology Group scale), measurable lesions, age between 18 and 70 years, white blood cells $\geq$4,000/mm^3; platelets $\geq$100,000/mm^3, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, γ-GT $\leq$2.5 $\times$ upper limit of normal, and bilirubin $\leq$3 mg/100 mL.

Patients with cardiac disease (congestive heart failure and history of myocardial infarction within the previous 3 months), severe vascular disease, or uncontrolled concomitant infections were excluded. Patients had baseline liver and renal function tests, electrolyte studies, and complete blood count done within 2 weeks of inclusion in the study. Also, bilateral mammography and ultrasound, chest X-ray, abdominal ultrasound, bone scan, serum CA 15.3 determination, and electrocardiography were performed within 2 weeks from the treatment start.

Each patient gave a written informed consent.

Treatment. Patients were treated with preoperative chemotherapy given in 3-week cycles. After each cycle disease was evaluated by clinical measurement of the two largest diameters. Surgery was planned in patients with clinically progressing disease. After three cycles, patients also had mammography and ultrasound breast examination to assess response. Patients with stable disease received surgery, and those with partial remission or complete remission were candidates to receive three more cycles of therapy, for a maximum of six cycles. The following regimens were used during the conduct of the study: (1) anthracycline containing regimens: ECF: E = Epirubicin 25 mg/m^2 i.v., days 1 and 2; C = Cisplatinum 60 mg/m^2 i.v. day 1; F = Fluorouracil 200 mg/m^2/day as continuous infusion days 1 to 21; AC/EC: A = doxorubicin 60 mg/m^2 or E = epirubicin 90 mg/m^2 i.v. day 1, C = cyclophosphamide 600 mg/m^2 i.v. day 1; (2) Taxane containing regimens: AT/ET: A = doxorubicin 60 mg/m^2 or E = epirubicin 90 mg/m^2 i.v. day 1, T = taxotere 75 mg/m^2 i.v. day 1; (3) Navelbine containing regimens: ViFuP: Vi = Vinorelbine (Navelbine) 20 mg total dose i.v. days 1 and 3; Fu = Fluorouracil 200 mg/m^2/day as continuous infusion days 1 to 21; P = (*cis*)Platinum 60 mg/m^2 i.v. day 1; FLN: F = Fluorouracil 350 mg/m^2 i.v. days 1 to 3; L = Lederfolin 100 mg/m^2 i.v. days 1 to 3; N = navelbine 20 to 25 mg/m^2 i.v. days 1 and 3. For regimens including continuous infusion FU, the insertion of a central venous catheter (Dome Port, Bard) was required, and infusion was provided by a Portable Elastomeric Infusion System (Baxter). Patients were instructed to change their own infusion bag every week.

Toxicity and Dose Modifications. Toxicity was evaluated according to National Cancer Institute of Cancer—Clinical Trials Group criteria by clinical and laboratory evaluations at day 21 of each cycle. If creatinine/blood urea nitrogen was up to 1.5, the upper normal value cisplatin was omitted. In case of constipation, mucositis, or diarrhea (grade $>$2), the next cycle of chemotherapy was postponed by 1 or 2 weeks until recovery and then administered at 75% of the dose. The treatment was postponed by 1 week if the blood count on day 21 showed a neutrophil count $<$1,000/mm^3 and/or platelet count $<$100,000 mm^3. If on day 28 the neutrophil count was $>$1,000/mm^3 and platelet count $>$100,000 mm^3, the treatment was readministered. Otherwise, treatment was postponed by another week. If after 2 weeks of treatment delay (on day 35) hematologic recovery (neutrophils $>$1,000 mm^3 and platelets $>$100,000/mm^3) was not obtained, treatment was discontinued.

Response Criteria. Responses were evaluated according to both radiologic (breast ultrasound plus mammography) and clinical evaluation and graded according to standard WHO criteria. Pathological complete remissions were evaluated according to Sataloff *et al.* criteria (15). A pathological complete remission was defined as a total or near total disappearance of the tumor. In particular, absence of invasive cancer or presence of isolated foci of invasive cancer both qualified for pathological complete remission. Axillary lymph nodes were also assessed independent of the primary tumor for the degree of pathological response according to the 5th Tumor-Node-Metastasis Staging System (16)

Pathology and Immunohistochemistry. This is a single institution study. All of the included patients had pathological evaluation performed at the European Institute of Oncology. The original receptor status determinations, performed before the study conduction, were used. Surgical specimens were extensively sampled for the evaluation of residual tumor after primary chemotherapy. In case of lack of macroscopic evidence of tumor the quadrantectomy specimens were entirely blocked in paraffin and examined histologically, as were the tumor-bearing quadrants of the mastectomies. In the latter cases, the other quadrants were also thoroughly evaluated with the examination of at least three tissue blocks.

Immunostaining experiments for the localization of estrogen and progesterone receptors, Her-2/*neu* protein, and Ki-67 antigen were performed on consecutive tissue sections of the tru-cut biopsies obtained before primary treatment and from the residual tumor after surgery, as reported previously (17). The following primary antibodies were used: the monoclonal

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antibody to estrogen receptor (Dako, at 1:100 dilution), the monoclonal antibody to progesterone receptor (Dako, 1:800), the MIB-1 monoclonal antibody to the Ki-67 antigen (Immunotech, Marseille, France, 1:1200), and the polyclonal antiserum (Dako, 1:3,200) to the Her-2/*neu* protein.

The immunostained slides were evaluated independently by two of the authors. Only nuclear reactivity was taken into account for estrogen receptor, progesterone receptor, and Ki-67 antigen, whereas only an intense and complete membrane staining >10% of the tumor cells was taken as evidence of Her-2/*neu* overexpression (3+). The results were recorded as the percentage of immunoreactive cells over at least 2,000 neoplastic cells. The median value of Ki-67 labeling index for the cohort of patients included in the study was used as a cutoff in distinguishing tumors with low (<25%) and high (≥25%) proliferative fraction. Steroid hormone receptors status was classified as absent (estrogen receptor and progesterone receptor 0% of the cells positive), low (estrogen receptor and/or progesterone receptor ≥1% <10% of the cells), or positive (estrogen receptor and progesterone receptor ≥10% of the cells).

Statistical Methods. The primary endpoints were achieving a pathological complete remission and node-negative status at final surgery. In addition, we evaluated the impact of estrogen receptor and progesterone receptor status and of the degree of response (pathological complete remission and node-negative status) on disease-free survival. We used logistic regression to model the probability of achieving a pathological complete remission first in univariate analyses and then in multiple regression analyses to identify the baseline factors that predicted a pathological complete remission. Similar analyses were performed for modeling nodal status to identify factors that predict node-negative status. Odds ratios, 95% confidence intervals (CI), and *P*s were estimated. The Wald test was used to evaluate significance of individual coefficients, and the likelihood ratio test was used to assess a factor with more than two levels (*e.g.*, tumor size). Factors included in the multiple regression analyses were menopausal status, estrogen receptor/progesterone receptor status, pathological grade, Ki-67, Her-2/*neu*, and treatment regimen. In addition, we explored all of the logistic regression models that included two baseline factors and the two-way interaction between those factors. Associations between categorical variables were assessed by a Fisher's exact test. Disease-free survival was calculated from the date of first treatment until breast cancer recurrence or a new breast cancer primary or death without recurrence, whichever occurred first. Results are available at a median follow-up of 3.8 years. Assessment of disease-free survival according to estrogen receptor/progesterone receptor status, pathological complete remission status, and nodal status were summarized using the 4-year disease-free survival percentage and the hazard ratio with the respective 95% CI. Cox multiple regression analysis was performed to assess factors predicting disease-free survival. $P < 0.05$ were considered to be statistically significant. No adjustment was made for performing multiple tests, and all of the probability values were two sided.

RESULTS

Of the 399 patients with response data, 15.7% had a pathological complete remission, 51.3% had objective clinical remission (complete remission + partial remission), 31.3% had stable disease, and 1.5% had progressive disease. As a result of the univariate analysis (Table 1), the factors that were significantly associated with pathological complete remission were estrogen receptor/progesterone receptor status ($P < 0.0001$), grade ($P < 0.0001$), Ki-67 ($P = 0.0001$), and infusional regimens ($P = 0.01$). Within the estrogen receptor/progesterone receptor absent cohort, 33.3% achieved a pathological complete remission compared with 7.4% and 7.6% within the estrogen receptor/progesterone receptor low and positive cohorts, respectively. The pathological complete remission percentage for patients with grade 3 tumors was 25.7% compared with 7.6% with grades 1 and 2. For patients with Ki-67 ≥ 25%, 22.3% achieved a pathological complete remission compared with 8.1% with Ki-67 < 25%. For patients that received infusional therapy, 19.5% had a pathological complete remission *versus* 10.1% for patients that received no infusional therapy. Differences in pathological complete remission rate according to whether or not an anthracycline was used were not statistically significant.

For the multivariate analysis, using logistic regression to model the probability of achieving a pathological complete remission, we combined the estrogen receptor/progesterone receptor-positive and estrogen receptor/progesterone receptor-low cohorts into one group. None of the two-way interactions were statistically significant.

Using a stepwise selection routine at the 0.05 significance level on all factors from the univariate analysis, estrogen receptor/progesterone receptor ($P < 0.0001$) and grade ($P = 0.001$) were the two factors that remained statistically significant in the model to predict pathological complete remission. Patients within the estrogen receptor/progesterone receptor absent cohort were 4.22 times (95% CI, 2.20–8.09, $P < 0.0001$) more likely to achieve a pathological complete remission than patients within the estrogen receptor/progesterone receptor-positive or-low cohort, and patients with grade 3 tumors were 3.36 times (95% CI, 1.62–7.01, $P = 0.001$) more likely to achieve a pathological complete remission compared with patients with grade 1 or 2 tumors.

A total of 388 (97%) patients had pathological examination of axillary lymph nodes. Of these 388 patients, 28.6% had node-negative disease at the time of final surgery. As shown in Table 2 a significant correlation between node-negative status and pathological complete remission was detected ($P < 0.0001$). As indicated in Table 1, the factors that were significantly associated with nodal status were estrogen receptor/progesterone receptor status ($P < 0.0001$), clinical tumor size ($P = 0.001$), and use of infusional regimens ($P = 0.003$).

Using logistic regression to model the probability of being node-negative at final surgery, none of the two-way interaction terms were statistically significant. The three factors that showed a significant association with nodal status in the univariate analysis were also the only three factors that were statistically significant in the multivariate analysis. Patients within the estrogen receptor/progesterone receptor-absent cohort were 3.47 times (95% CI, 2.09–5.76, $P < 0.0001$) more likely to have node-negative disease at final surgery than patients within the estrogen receptor/progesterone receptor-positive or -low cohort, and patients with T2 tumors were 4.0 times (95% CI, 2.02–7.87, $P < 0001$) more likely to have node-negative disease than

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Table 1 Pathological complete remissions and nodal status at definitive surgery according to baseline factors

Baseline factor	Response			Nodal status		
	Total	Pathological CR % (*N*)	*P*	Total	Node-negative % (*N*)	*P*
Total	399	15.7 (63)		388*	28.6 (111)	
ER/PgR						
Absent	129	33.3 (43)	<0.0001	126	42.9 (54)	<0.0001
Low†	94	7.4 (7)		91	28.6 (26)	
Positive	171	7.6 (13)		167	18.0 (30)	
Unknown	5	0.0 (0)		4	25.0 (1)	
Menopausal status						
Premenopausal	210	14.7 (31)	0.58	206	25.7 (53)	0.22
Postmenopausal	189	16.9 (32)		182	31.9 (58)	
Clinical tumor size						
T2	235	14.8 (35)	0.81	227	35.7 (81)	0.001
T3	74	17.5 (13)		74	21.6 (16)	
T4	90	16.6 (15)		87	16.1 (14)	
Grade						
Grades 1,2	143	7.6 (11)	<0.0001	141	30.5 (43)	0.99
Grade 3	159	25.7 (41)		157	30.6 (48)	
Unknown	97	11.3 (11)		90	22.2 (20)	
Ki-67						
<25%	172	8.1 (14)	0.0001	164	25.6 (42)	0.35
≥25%	210	22.3 (47)		208	30.3 (63)	
Unknown	17	11.7 (2)		16	37.5 (6)	
Her-2/*neu*						
Intense and complete	51	21.5 (11)	0.28	50	38.0 (19)	0.39
Other	154	14.9 (23)		148	31.1 (46)	
Unknown	194	14.9 (29)		190	24.2 (46)	
Infusional						
Infusional therapy	241	19.5 (47)	0.01	234	34.2 (80)	0.003
No infusional therapy	158	10.1 (16)		154	20.1 (31)	
Regimen						
Antracyclines	212	15.5 (33)	0.87	203	29.6 (60)	0.46
Antracyclines and taxanes	15	20.0 (3)		15	13.3 (2)	
Others	172	15.6 (27)		170	28.8 (49)	

* 11 cases did not have axillary lymph nodes examined.
† Defined as estrogen receptor and/or progesterone receptor >1% <10% of the cells.

patients with T4 tumors, and patients who received infusional therapy were 2.14 times (95% CI, 1.29–3.57, $P = 0.003$) more likely to have node-negative disease than patient treated with no infusional therapy.

We also evaluated the correlation between Her-2/*neu* overexpression and response to anthracycline-containing chemotherapy. A slight increased pathological complete remission rate was observed for tumors overexpressing Her-2/*neu* (33 patients) *versus* those not overexpressing Her-2/*neu* (115 patients), although this was not statistically significant (27.3% *versus* 16.5%, $P = 0.21$). In regimens not containing anthracyclines, the pathological complete remission rate was similar for Her-2/*neu* overexpressing tumors (18 patients) and for tumors not overexpressing Her-2/*neu* (39 patients, 11.1% *versus* 10.3%, $P = 0.99$). The interaction between Her-2/*neu* and chemotherapy regimen was not statistically significant ($P = 0.82$). Eighty-seven percent of the 336 patients who did not have a pathological complete remission were assessable for estrogen receptor and progesterone receptor at both baseline and final surgery. The changes in estrogen receptor and progesterone receptor category are shown in Table 3. Estrogen receptor status changed for 9% of the patients (both pre- and post-menopausal), whereas progesterone receptor status changed for 26% of premenopausal patients and 30% of postmenopausal patients. In the present study no significant correlation between modification in the expression of biological features and clinical response was detected, in particular for Ki-67 expression (data not shown).

Despite the significantly higher incidence of pathological complete remission and node-negative status achieved by preoperative chemotherapy for patients with estrogen receptor and progesterone receptor-absent disease, the disease-free survival was significantly worse for this cohort compared with the low/positive expression cohort (4-year disease-free survival: 41% *versus* 74%, hazard ratio, 3.22; 95% CI, 2.28–4.54; $P < 0.0001$; Fig. 1.). Patients who achieve pathological complete remission had a nonstatistically significant worse disease-free

Table 2 Correlation between pathological complete remission and nodal status

	PCR		cCR/cPR		Stable disease		*P*
	%	(*N*)	%	(*N*)	%	(*N*)	
Node-negative	58	(35)	28	(56)	16	(19)	
Node-positive	42	(25)	72	(145)	84	(103)	<0.0001
Total	100	(60)	100	(201)	100	(122)	

Abbreviations: cCR, complete remission; cPR, partial remission.

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Table 3 Changes in ER and PgR expression during chemotherapy (from baseline to final surgery) according to menopausal status

	ER premenopausal		PgR premenopausal		ER postmenopausal		PgR postmenopausal	
	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*
Total assessable* c	100	(166)	100	(166)	100	(128)	100	(127)
Unchanged	91	(151)	73	(122)	91	(117)	70	(89)
Changed	9	(15)	26	(44)	9	(11)	30	(38)
Types of change								
Pos → Low	1	(2)	4	(6)	1	(1)	6	(8)
Pos → Absent	3	(5)	13	(22)	3	(4)	9	(11)
Low → Pos	1	(2)	2	(4)	0	(0)	2	(3)
Low → Absent	1	(2)	1	(2)	1	(1)	1	(1)
Absent → Pos	2	(4)	5	(8)	4	(5)	6	(8)
Absent → Low	0	(0)	1	(2)	0	(0)	6	(7)

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor, pCR, pathological complete remission.
* Patients with pCR who have ER and PgR values available at both baseline and final surgery.

survival (57%) than patients who did not achieve pathological complete remission (64%; hazard ratio, 1.29; 95% CI, 0.83–2.00; $P = 0.26$), possibly due to the higher proportion of receptor absent disease in the pathological complete remission group. Patients who achieve node-negative disease at final surgery had significantly better disease-free survival than patients with node-positive disease (4-year disease-free survival %: 77% *versus* 60%; hazard ratio, 0.51; 95% CI, 0.31–0.82; $P = 0.005$). In the Cox multiple regression analyses, the receptor status of the primary tumor was the most significant predictor of disease-free survival.

DISCUSSION

The most relevant factors for the estimation of risk of recurrence in patients with early breast cancer after radical surgery are nodal status, number of nodes involved, presence of vessel invasion, tumor size, grade, and age (18, 19). Determination of steroid hormone receptor expression in the primary tumor is a factor that is mainly used to predict endocrine responsiveness. Specifically for patients with node-negative disease, pathological tumor size, grade, and age are factors considered important for such risk assessment, thus influencing choice among different treatment options, together with the status of endocrine responsiveness. Regrettably, the success of adjuvant treatment can only be postulated when patients remain free of disease after several years. Conversely to the method used to choose an adjuvant systemic therapy regimen, the selection of preoperative therapy does not commonly take into account biological characteristics of the tumor. In fact, very few features were tested as predictors of preoperative treatment response indicators, including diameter of the tumor (20) and in very few patients MIB-1 increased expression (17, 21) or proliferative index (22, 23). A large experience on factors predicting response in the preoperative setting was published recently and is based on a retrospective analysis of the National Surgical Adjuvant breast and Bowel Project B-18 study (24). The evaluation was performed on 493 patients [fine needle aspiration cytology of 450 patients and/or sections of core biopsy (Tru-cut) in only 61 cases]. In this trial in which steroid hormone receptors were not determined in either patients with fine needle aspiration cytology or those with Tru-cut, the poor nuclear grade significantly predicted a pathological complete remission. Similar results were obtained by using nuclear and histologic grade on core biopsy material in our series.

Change in the expression of biological features after exposure to the systemic treatment and their possible correlation with clinical response was studied in small cohorts of patients receiving primary chemotherapy. Published trials on patients treated with preoperative chemotherapy or chemoendocrine therapies showed a positive association between Ki-67 reduction with treatment and response (25–27). In the present study no significant correlation between modifications of the expression of biological features and clinical response was detected. A slight change in steroid hormone expression, in particular progesterone receptor expression, was observed. A possible explanation for the changes in estrogen receptor/progesterone receptor ex-

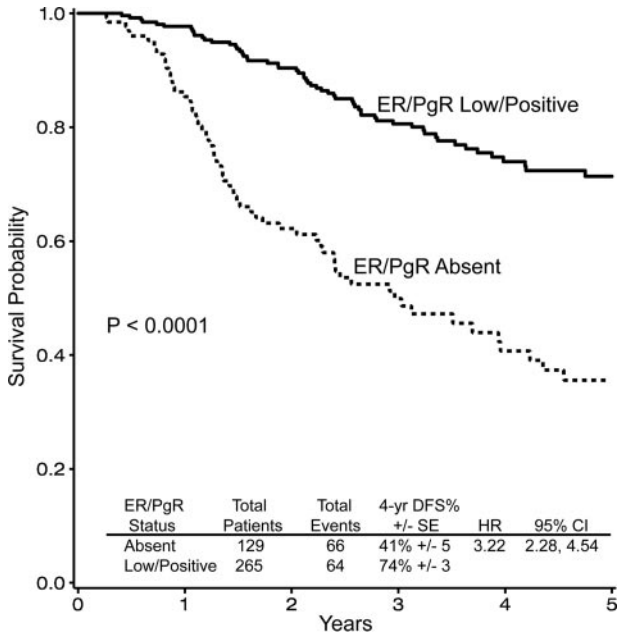

Fig. 1 Kaplan-Meier plot of DFS according to ER/PgR status of the primary tumor. Results are reported at 3.8 years of median follow-up. DFS, disease-free survival; HR, hazards ratio; ER, estrogen receptor; PgR, progesterone receptor.

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pression might be related to tissue sampling issues as indicated in a small study from Lee *et al.* (28). It is noteworthy, however, that premenopausal-aged women were likely to achieve an endocrine effect with chemotherapy through ovarian function suppression (29). Also, postmenopausal-aged women may obtain some additional endocrine effect from suppression of adrenals (30) due to cytotoxics and steroids. These endocrine actions of chemotherapy might be the reason for the observed changes in the expression of steroid hormone receptors.

The relationship between steroid hormone receptor expression and response to chemotherapy has received little attention in the past. Two decades have passed since this relationship was debated with the presentation of conflicting reports in the metastatic setting (31, 32). Limited data are available on the relationship between number of cells expressing hormone receptors and response to chemotherapy in the preoperative setting. This might be explained by the heterogeneity of examinations, methods, and especially cut-offs used in the various studies. The results of initial immunohistochemical assessment of p53, Her-2/*neu*, glutathione *S*-transferase, Ki-67, pS2, and estrogen receptor/progesterone receptor in baseline core biopsy samples of 134 patients from the Bordeaux randomized trial showed that estrogen receptor-negative status (defined at immunohistochemical evaluation as estrogen receptor $<10\%$ of the cells) and high Ki-67 were correlated with clinical tumor response (21). Interestingly, when the analysis was conducted with the dextran-coated charcoal method, less estrogen receptor-positive tumors were detected compared with immunohistochemistry (46% *versus* 67%), and no significant correlation was detected between response and estrogen receptor status. A more recently published trial showed a significantly higher pathological response rate for estrogen receptor-negative tumors (defined as $<10\%$ of the cells) compared with estrogen receptor-positive tumors (25). The largest experience on hormone receptor expression predicting response in the preoperative setting was published recently and is based on an analysis of the National Surgical Adjuvant breast and Bowel Project B-27 study (13). Overall, estrogen receptor-negative tumors had higher pathological response rates than did estrogen receptor-positive tumors (16.7% *versus* 8.3%, respectively, $P = 0.001$). A test of estrogen receptor status by treatment interaction was not significant ($P = 0.69$), indicating that estrogen receptor status had little effect on the ability of preoperative docetaxel to improve pathological response. In the trials described above, analyses were performed based on a so-called "receptor-negative grouping," which combines receptor-absent disease with that expressing low receptor levels. In the present study, which represents the largest available analysis conducted by the same team of pathologists on pretreatment biopsies, we demonstrated a different pattern of response to chemotherapy for endocrine nonresponsive disease (defined as steroid hormone receptor absent tumor). Some clinical studies (33) and gene expression profiling (34, 35) already provide empirical data that receptor-absent breast cancer is a distinct entity from that with even low levels of receptor expression.

In the present study both the pathological complete remission rate and the frequency of node-negative status at final surgery were significantly higher after preoperative chemotherapy for patients whose tumors did not express estrogen receptor and progesterone receptor, compared with the receptor-expressing cohort. This emphasizes the chemoresponsiveness of tumors that do not express any estrogen receptor or progesterone receptor. Despite the high pathological complete remission rate and node-negative status, the disease-free survival at 3.8 years of median follow-up was significantly worse for the receptor-absent compared with the receptor-present groups. The responsiveness of tumors expressing some receptors to endocrine therapies (*e.g.*, ovarian function suppression, tamoxifen, and aromatase inhibitors) might explain the different outcome observed. In fact, after surgery patients with endocrine unresponsive disease generally did not received additional systemic therapy, whereas those with endocrine-responsive disease received additional endocrine treatment postoperatively. These findings provide substantial additional evidence to support the hypothesis that steroid hormone receptor status of the primary tumor defines distinct biological entities that require a differentiated approach to treatment and clinical trial investigation. Separate analyses according to steroid hormone receptor status must be prospectively planned for future clinical trials and conducted for current and past studies whether or not these were prospectively included in the protocol.

The efficacy of systemic therapy for early breast cancer depends on features of the treatment as well as the tumor and the patient. The introduction of taxanes provided encouraging results in recent trials in the preoperative setting. Smith *et al.* (14) reported higher pathological complete remission rate on patients with large or locally advanced breast cancer who, after four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone, received four courses of taxotere *versus* four additional courses of cyclophosphamide, doxorubicin, vincristine, and prednisolone (34% *versus* 16%, respectively, $P = 0.04$). In the National Surgical Adjuvant breast and Bowel Project B-27 the addition of 4 cycles of taxotere after 4 cycles of AC significantly improved pathological complete remission from 13.7% to 26.1% (13). Whereas no information on response and endocrine responsiveness is available for the former trial, in the National Surgical Adjuvant breast and Bowel Project trial the results across all of the age groups are not informative concerning chemosensitivity of the use of taxanes for estrogen receptor-positive disease. Fifty-six percent of the patients were ≤ 49 years old, and 30% were in the 50 to 59 age group. It is likely that more than two thirds of the patients were premenopausal, and differential endocrine effects of the chemotherapy regimens contributed to the finding in the estrogen receptor-positive cohort. Furthermore, because tamoxifen was given concurrently with chemotherapy, the tamoxifen duration was either 24 weeks or 12 weeks according to treatment assignment making comparisons for the receptor-positive cohort quite problematic. In addition, mixing estrogen receptor absent and estrogen receptor-low tumors together in the category labeled as estrogen receptor-negative attenuates the chemosensitivity that might have been observed in the truly endocrine unresponsive cohort.

In conclusion, the present study indicates the importance of preoperative chemotherapy for patients with estrogen receptor- and progesterone receptor-absent tumors, as well as the poor outcome in terms of disease-free survival for this patient population. Additional studies using database analyses or prospective trials are required to confirm the value and limitations of primary chemotherapy in endocrine nonresponsive tumors. If

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confirmed, future selection of preoperative treatment should be based on tumor characteristics such as estrogen receptor and progesterone receptor status, and the current practice of many laboratories to report receptor status as merely positive or negative should change to a more quantitative reporting of routine receptor determinations to identify the estrogen receptor and progesterone receptor-absent cohort.

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Chemotherapy Is More Effective in Patients with Breast Cancer Not Expressing Steroid Hormone Receptors: A Study of Preoperative Treatment

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