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Estrogen-receptor Status and Response to Chemotherapy in Early and Advanced Breast Cancer*

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Summary. *The value of estrogen receptor (ER) status in the prediction of tumor response to combination chemotherapy was retrospectively analyzed in breast cancer patients selected for prospective controlled trials of chemotherapy (85 with advanced disease and 256 with operable tumors). All patients were previously untreated with either chemotherapy or endocrine therapy, and in all instances drug therapy was applied at the time of primary treatment. The ER status was considered positive in 54% of women with advanced disease and in 70% of women with operable breast tumor and positive axillary nodes, respectively. About 12% of patients were considered to have borderline ER. The response to drug therapy (complete plus partial remission in advanced breast cancer and 3-year relapse-free survival after mastectomy, respectively) was not significantly different between ER+ and ER− tumors. The comparative results of ER+ vs ER− patients were similar whether the cutoff point for ER+ tumors was > 5 or > 10 fmol/mg cytosol protein. The present results indicate that in advanced and early breast cancer combination chemotherapy is effective regardless of ER status. Therefore, in the presence of ER+ tumors there is no reason to delay the early administration of effective chemotherapy. This is particularly true both in the presence of rapidly progressing metastatic disease and in the adjuvant setting.*

Introduction

The significance of estrogen receptors (ERs) in prediction of the objective response to endocrine therapy in advanced breast cancer has been extensively evaluated in a number of studies [16]. There may be considerable assay variations between different laboratories, and even within the same laboratory, and the cutoff point distinguishing negative from positive specimens is still the subject of discussion. However, despite these limitations, the assays for cytoplasmic ER have been found clinically useful for identification of hormone-responsive tumors. The correlation between receptor values above three femtomoles (fmol) per milligram of cytosol protein and tumor response rate is high, ranging from 45% to 80%, depending on the actual quantitative amount of estrogen receptor in the tumor specimen [16].

More recently, hormone receptor status has been correlated with responsiveness to cytotoxic chemotherapy in patients with advanced breast cancer [12, 13, 15] and with relapse free and total survival rates following mastectomy [1, 5, 14, 16, 19, 24]. In all published series the ER status correlated with the short-term relapse-free survival (RFS), i.e., ER-negative (ER−) tumors recurred earlier than ER-positive (ER+) patients, probably because ER− tumors have a higher growth rate [18]. In contrast, the comparative results in advanced disease treated with chemotherapy appear widely divergent and contradictory. Most probably, the differences are due to numerous factors, viz., different assay criteria for positive ER, prognostic variables, drug regimens used, and response criteria [4]. This paper reports the correlation between ER status and response to combination chemotherapy in patients with advanced breast cancer and in patients with operable tumors. For the latter group the prognostic value of ER has not yet been reported after adjuvant treatment. To avoid or at least minimize the influence of known prognostic variables, the study was undertaken in patients selected for prospective controlled clinical trials of combination chemotherapy and had received no previous treatment with chemotherapy and/or endocrine therapy.

Patients and Methods

Patient Characteristics

The series comprises two groups of patients, in which the extent of disease is different (Table 1). The first group includes 85 women with

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Table 1. Patient characteristics

Disease extent	No.	Percentage			Drug combinations
		ER+	ER−	ER±	
Inoperable	85	54	35	11	
Metastatic	7	43	57	0	CMF ± AV
T_{3b}–T_4	68	58	32	10	AV
Inflammatory Ca	10	40	40	20	CAFP
Operable	256	70	18	12	
Premenopausal	193	72	17	11	CMF
Postmenopausal	63	63	21	16	CMF

inoperable breast cancer. Most patients (80%) were classified according to the UICC system as T_{3b}–T_4 (tumor > 5 cm in its greatest dimension, with fixation to underlying pectoral fascia and/or muscle or tumor of any size with direct extension to chest wall or skin). Ten patients had local disease infiltrating intradermal lymphatics (inflammatory carcinoma) and seven patients had clinical and/or radiological evidence of metastatic cancer in distant organs and tissues. However, all the lesions were in soft tissue (breast, skin, lymph nodes) except in one patient, who, besides involvement of the breast, also had lytic skeletal metastases. In 62 of 78 (79%) women with either T_{3b}–T_4 or inflammatory carcinoma the axillary lymph nodes were also clinically involved. The second group of patients includes 256 women with primary operable breast cancer (UICC classification: T_{1a}–T_{2a}–T_{3a}), in whom the axillary lymph nodes were found on histologic examination to be positive after radical or modified radical mastectomy.

Drug Treatment

All patients were previously untreated with chemotherapy or endocrine therapy. Thus, the drug regimens utilized represented the first systemic treatment for disseminated disease (7 patients) and the first multimodality approach with either initial chemotherapy followed by local therapy (78 patients) or with adjuvant chemotherapy following mastectomy (256 patients). In disseminated breast cancer, chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil) alone or alternating with AV (adriamycin plus vincristine) was administered until there was clinical and/or radiological evidence of tumor progression. In patients with T_{3b}–T_4 the response to chemotherapy was evaluated after three cycles of AV, i.e., before randomization to mastectomy or radiotherapy. In women with inflammatory carcinoma, the CAFP regimen (cyclophosphamide, adriamycin, fluorouracil, prednisone) was given for six cycles unless disease progression occurred earlier. In operable breast cancer CMF adjuvant chemotherapy was administered for twelve or six monthly cycles after mastectomy (Table 1). The details of drug treatment for each subgroup have been published elsewhere [2, 3, 7, 23].

Assessment of Response

Drug response was assessed without knowing the ER status. In patients with inoperable breast carcinoma the objective criteria utilized were those recently proposed on an international basis [10]. In particular, complete remission was defined as the disappearance of all symptoms and signs of disease for a minimum of 1 month, including recalcification of all osteolytic metastases. Partial remission was defined as tumor regression of at least 50% in the product of the two largest perpendicular diameters of all measurable lesions, with partial recalcification of osteolytic metastases, associated with improvement in evaluable but nonmeasurable lesions for a minimum of 1 month. Measurable tumor regression by less than 50% was considered as no response. In women receiving adjuvant CMF, drug response was measured in terms of RFS at 3 years from mastectomy after systematic follow-up studies. Whenever technically feasible, the first treatment failure was also documented through biopsy.

ER Determination

The ER content was determined on the primary tumor by use of the dextran-coated charcoal method according to the EORTC group [8, 9]. The binding parameters (ER concentration or femtomoles per milligram protein and association constant or Ka) were determined through Scatchard analysis. Levels below 5 fmol/mg cytosol protein and Ka < $1.5 \times 10^9\ M^{-1}$ were regarded as negative. In a series of patients with advanced breast cancer who had ER+ tumors and were treated by hormonal manipulations, complete or partial remission occurred in 47.3% of 19 women subjected to therapeutic castration and in 46.1% of 13 women given tamoxifen, respectively. This correlation in terms of response to endocrine therapy provides adequate vindication of the method used in our laboratory for ER assay. In the present series, ER+ tumors accounted for a total of 225 women (66%). Patients with borderline estrogen receptors (ER±) made up about 12% of the entire series (Table 1). In ER+ tumors the median level of fmol/mg was 29.5 (range 5–800) for premenopausal women and 79.5 (range 7.6–1,619) for postmenopausal women, respectively.

Statistical Analyses

Tests of significance on the type of response in advanced disease were done with the χ^2-test (with correction for continuity in small subgroups).

The actuarial life-table method has been utilized to summarize both RFS and overall survival distributions starting from the date of mastectomy in operable cancer and from the date of initial treatment for advanced disease, respectively. The statistical significance of differences observed between ER+ and ER− populations has been assessed by the Mantel-Haenszel test for survivorship data [17]. The percentages of patients free of disease or surviving are reported in the text and in the tables for one point in time (2 years for advanced and 3 years for operable cancers), as derived from the life-table plots, while the *P* values quoted represent comparison of the entire curves.

Results

Irrespective of ER status, complete or partial remission occurred in 52% of 85 patients with measurable breast cancer (disseminated disease 43%, T_{3b}–T_4 extent 53%, inflammatory carcinoma 50%), with no significant difference between pre- (50%) and postmenopausal (52%) women. The results were comparable to those obtained in our previous experience [3, 6]. The limited number of patients with disseminated disease (7 cases) probably accounted for the somewhat low response rate observed in this subgroup. There was no statistical difference in the incidence of complete or partial response between ER+ (52%) and ER− (53%) tumors ($P = 0.89$). This was also true when the response rate was related to menopausal status and disease extent (Table 2). The response rate in

Table 2. Measurable breast cancer: Response to chemotherapy related to ER status

Disease extent	No.	Percentage objective response			P^a
		ER+	ER−	ER±	
Premenopausal	47	58	53	37	0.85
Metastatic	5	33	50	–	0.58
T_{3b}–T_4	35	63[b]	50	50	0.78
Inflammatory Ca	7	50	67	0	0.58
Postmenopausal	38	45	53	100	0.90
Metastatic	2	–	50	–	–
T_{3b}–T_4	33	45[b]	50	100	0.93
Inflammatory Ca	3	50	100	–	0.67

[a] ER+ vs ER−
[b] T_{3b}–T_4 with ER+: Pre- vs post-, $P = 0.42$
Total with ER+: Pre- vs post-, $P = 0.79$

Table 3. 3-year relapse-free survival after adjuvant CMF related to ER status

Disease extent	No.	Percent relapse-free			P^a
		ER+	ER−	ER±	
Premenopausal	193	82.9	78.2	70.6	0.23
Nodes: 1–3	104	96.3	81.9	79.0	0.13
> 3	89	68.8	61.2	59.6	0.52
CMF amenorrhea[b]	131	87.2	71.3	70.1	0.16
No amenorrhea[b]	37	77.5	62.5	–	0.60
Postmenopausal	63	81.9	75.2	100	0.82
Nodes: 1–3	42	85.3	83.4	100	0.60
> 3	21	74.1	66.7	100	0.90

[a] On time distribution (ER+ vs ER−)
[b] Patients with last menstrual period prior to mastectomy are excluded

the limited number of patients with ER± ranged from 0% to 100%. When a cutoff point of > 10 fmol/mg was used the comparative analysis failed to show a statistical difference in the response rate between ER+ and ER− tumors. In women with metastatic and with inflammatory carcinoma the duration of response was not different between ER+ and ER− tumors, being in excess of 10 months for both groups. Nor was the 2-year overall survival statistically different between patients with ER+ (86.1%) and ER− (72.7%) tumors ($P = 0.15$). There was only a trend for improved 2-year survival in premenopausal women with ER+ (91%) compared with premenopausal women with ER− (56%) tumors ($P = 0.12$). The corresponding findings for postmenopausal women were 81.9% and 78.8%, respectively ($P = 0.50$).

In the series of operable breast cancer patients in whom ER determination could be performed at the time of radical mastectomy, the 3-year actuarial analysis revealed that, irrespective of ER status, there was no significant difference between patients who received twelve and those who received six cycles of adjuvant CMF. In 193 premenopausal women the RFS was 83.9% for those who received 12 cycles, as against 84.8% for patients given six cycles. The total survival rates were 87.8% and 86.2%, respectively. In 63 postmenopausal women the RFS was 85.2% after 12 cycles and 75.2% after six cycles ($P = 0.39$). The corresponding figures for total survival were 92.4% and 84.7%, respectively ($P = 0.44$). This lack of difference was also observed between pre- and postmenopausal women in both major nodal subgroups (1–3 and > 3).

Due to the lack of difference in therapeutic results and our knowledge that other prognostic variables, such as size of primary tumor, number of involved axillary nodes, and especially ER status were comparable between the two groups receiving twelve or six cycles of CMF, the patients were grouped in a single series. Furthermore, a detailed analysis failed to reveal that the duration of adjuvant treatment affected the RFS when related to ER status. Table 3 shows that at 3 years after radical mastectomy the RFS was similar for ER+ and for ER− tumors, regardless of menopausal status. In particular, for ER+ and ER− tumors the RFS was comparable both in the two major nodal subgroups and in patients with and without CMF-induced amenorrhea. The latter finding definitely rules out the hypothesis that in premenopausal women the therapeutic effect of CMF is largely, if not exclusively, related to chemical castration [2]. In this series, patients with ER± tumors showed a high 3-year survival and none of the ten postmenopausal patients relapsed. The results remained essentially unchanged when the cutoff point of > 10 fmol/mg was utilized. The 3-year overall survival after adjuvant CMF revealed that the total difference between ER+ (90.8%) and ER− (78.2%) tumors was not significant ($P = 0.10$). However, there was a statistically higher 3-year survival of premenopausal women with ER+ (88.5%) than of premenopausal women with ER− (72.1%) tumors ($P = 0.01$). The corresponding findings for postmenopausal women were 91.7% and 84.2%, respectively ($P = 0.45$).

Discussion

The results of this retrospective analysis failed to demonstrate that in untreated breast cancer the ER status per se predicts for chemotherapy response. This was true in both advanced and operable disease with positive axillary lymph nodes. As far as advanced breast cancer is concerned, our findings are a contrast to those published by Lippman et al. [15] and Jonat et al. [12], who have claimed that ER values are an important predictor of

response to cytotoxic chemotherapy. Similarly, our results are different from those of Kiang et al. [13], who found that the response rate to chemotherapy was significantly higher in receptor-"rich" tumors than in receptor-"poor" tumors. As stressed by Carter [4], the explanation for the contradictory results of the above-mentioned studies lies in the heterogeneity of patient material and, most probably, also in different response criteria and data-reporting techniques, leading to lack of comparability.

In advanced breast cancer important areas for comparability analysis are usually represented by clinical prognostic variables (e.g., disease-free interval, menopausal status, visceral versus nonvisceral extent of disease, prior endocrine and/or cytotoxic therapy), treatment regimens, and criteria for assessment of objective response. For this reason, contrary to what has been reported in the NCI [15] and Minnesota [13] series, we have included in our analysis a more uniform group of patients. In fact, patients were all previously untreated and were examined in controlled studies, while the disease was confined to soft tissues except in one patient, thus making objective evaluation more simple and uniform. Finally, the type of drug regimen was limited to three combinations, which yielded a comparable response rate in the various subsets. Although not ideal, this type of patient selection has probably minimized most of the heterogeneous factors present within the NCI and Minnesota series [13, 15]. The above-mentioned series and our own are not comparable in terms of ER assay. The methods and the timing of receptor assay in the clinical course of the disease were different. Furthermore, the breakdown in the percentage of ER+ vs ER− tumors was also different, as was the cutoff point for the determination of ER positivity. However, for the sake of comparability with at least one series [15] we have evaluated our results according to two different levels of fmoles (> 5 vs > 10) and found no appreciable difference between the two types of analysis. Although not strictly comparable, our findings in advanced breast cancer are more in line with those recently reported by other investigators [11, 20, 22], showing that the ER status does not appear to be an important determinant of response to chemotherapy.

In the adjuvant situation, CMF chemotherapy appeared effective regardless of the number of cycles administered (12 or 6), drug-induced amenorrhea, menopausal status, and ER status. Here too, the results for ER+ tumors were not substantially different when the two levels of fmoles (> 5 or > 10) were considered. The only prognostic indicator for the 3-year RFS consisted in the classic breakdown of histologically involved axillary lymph nodes (1–3 vs > 3). Again, our results run counter to previous findings, i.e., following radical mastectomy women with ER− tumors have a shorter disease-free interval than women with ER+ tumors. In fact, in our series, the constant trend in the RFS favoring ER+ tumors was never statistically significant in any of the subgroups examined. Therefore, our results strongly suggest that when effective adjuvant combination chemotherapy is applied, the reported prognostic difference between ER+ and ER− tumors becomes negligible. The observation that breast cancer is responsive to cytotoxic drugs regardless of receptor status is further substantiated by the finding that the 3-year RFS after mastectomy in our patients with ER+ and ER− tumors is higher than that in women who have had axillary metastases and been treated only by surgery [5]. However, the hypothesis of some preferential effect of chemotherapy for ER− tumors cannot be entirely ruled out in an adjuvant setting. The statistically higher 3-year total survival in the subset of premenopausal women with ER+ tumor than in women with ER− tumors is somewhat difficult to interpret, since the comparative RFS was not different. In our opinion, this difference, which was not observed in the postmenopausal group, could be related more to the site(s) of recurrence and response to secondary therapy than to ER status per se.

In conclusion, while endocrine treatment alone remains a useful tool for many women with ER+ tumors, there should be no contraindication to effective chemotherapy early in the treatment of breast cancer in the presence of positive receptors. This is particularly true in patients with rapidly progressing metastatic disease and in patients who are candidates for adjuvant therapy. Recent findings [21] showing that in both pre- and postmenopausal women the 4-year RFS and total survival rates are also related to the percentage of adjuvant CMF administered (less or greater than 75%) strongly support this contention. Therefore, the traditional schematic approach — endocrine therapy alone for ER+ tumors and chemotherapy only in the presence of ER− tumors — should be critically re-evaluated, if not totally abandoned.

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