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Steroid Hormone Receptors and Disease: Breast Cancer (40610)

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Breast cancer is the leading cause of cancer death in women today. Although more than 90,000 new cases are diagnosed and 30,000 women die annually from breast cancer, few major advances have occurred in our understanding of the disease or its treatment until recently. In the past few years, however, basic laboratory research into the factors controlling breast cancer cell growth has been rewarded with significant new information applicable to the clinical care of patients. In fact, as a direct result of laboratory investigation, our approach to the management of this malignancy has changed dramatically. It is the purpose of this review to highlight some of the recent advances on the use of steroid receptors in the management of breast cancer patients and pinpoint the need for future clinical trials.

Cytoplasmic estrogen receptor in primary breast cancer. The most useful criterion to predict the likelihood of recurrence following mastectomy for primary breast cancer is the axillary node status. Patients with tumor-infiltrated axillary nodes are at high risk of returning with metastatic disease (2). This finding has led to the introduction of systemic therapies following mastectomy in node-positive patients to delay or prevent recurrences. Since estrogen receptor (ER) assays have been used with considerable success to predict responsiveness to endocrine therapy in patients with advanced disease (13), it was reasoned that they might be similarly useful in deciding whether or not to include endocrine therapy in an adjuvant regimen. Previous attempts of adjuvant endocrine therapy have been disappointing but probably were inconclusive since stratification of patients according to ER status had not done. As an effort preliminary to an actual adjuvant trial, a series of 145 patients with operable breast cancer and an ER assay of the primary tumor specimen were examined for recurrence and survival (9). The data are unambiguous and are illustrated in Table I. Irrespective of age, nodal status, size of tumor, or location of the tumor in the breast, patients with ER− tumors recurred earlier than ER+ patients. In a recent update of this series (10), Knight and colleagues showed that survival is adversely affected as well in patients with ER− tumors, confirming an earlier report by Walt *et al.* (20). Thus, the ER status of the primary tumor is a useful marker of the biological aggressiveness of the disease.

What then are the implications for adjuvant therapy? We note that in the two most widely publicized trials of adjuvant chemotherapy (1, 3), delay in recurrence is confined to premenopausal women. Since 78% of premenopausal patients receiving combination chemotherapy developed amenorrhea (1), and Rose and colleagues showed that the same drug regimen caused decreased ovarian steroid production and elevated gonadotropin production (17), it is tempting to suggest that the benefits of cytotoxic adjuvant therapy in premenopausal patients are due to drug-induced ovarian failure. However, a recent preliminary report (19) indicates that chemotherapy-induced ovarian failure occurs only in premenopausal patients over the age of 40 and could not explain the delay in recurrence observed in younger patients receiving chemotherapy.

An alternative line of reasoning might be considered to explain the chemotherapy benefits in premenopausal women. First, compared to older patients, premenopausal patients are more likely to have ER− tumors; those with ER+ tumors have considerably lower absolute ER values, implying a greater precentage of ER− cells within the tumor. Next, ER− tumors have a higher thymidine labeling index than ER+ tumors, indicating that more cells within the tumor are undergoing DNA synthesis (16). This would support the clinical observations referred to above that ER− tumors are more aggressive in their

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growth behavior. Since in many tumor systems it has been shown that tumors with the most rapid doubling times are the most sensitive to chemotherapy, the idea emerges that ER− tumors should be most responsive to chemotherapy.

So then what are the questions to be answered regarding receptor status and adjuvant therapy? As shown in Table II we would initially divide node-positive patients into ER− and ER+ groups instead of the usual classification of pre- and postmenopausal. This makes the assumption that tumor aggressiveness and response to both endocrine and chemotherapy are determined primarily by ER status rather than menopausal status. This represents a departure from traditional thinking, but in view of the arguments listed above it may have considerable merit. ER− patients will not respond to endocrine therapy and the data of Meyer *et al.* (16) indicate that these aggressive ER− tumors have high thymidine labeling indices which should respond to chemotherapy. Since no benefit has yet been shown in postmenopausal patients from adjuvant therapy, a placebo group is justified.

In ER+ patients we consider menopausal status because of the important ovarian source of estrogens and the results of current adjuvant trials showing a benefit from chemotherapy only in the premenopausal group (1, 3). Premenopausal patients who have ER+ tumors would be randomized between an endocrine therapy and combination chemotherapy. The logical choice for endocrine therapy would be ovariectomy to remove ovarian sources of estrogens. However, it is well known that when patients with advanced disease eventually relapse following ovariectomy, another objective remission can be obtained by removing the adrenal glands. The rationale is that the adrenals secrete appreciable quantities of androstenedione which is peripherally converted to estrogen, resulting in tumor growth. So in addition to ovariectomy we might use another tactic to decrease adrenal androstenedione production or block its effect at the tumor cell. Either approach is feasible and has been demonstrated to be effective. The combination of aminoglutethimide and hydrocortisone can effectively block adrenal estrogen precursor production and induce tumor regression in postmenopausal women (18). Alternatively, the estrogen derived from the adrenal can be prevented from stimulating tumor cell growth by antiestrogens, a relatively new class of compounds which exert their effects at the ER level in tumor cells (5). In view of the above, a combination of ovariectomy plus either antiestrogen or aminoglutethimide and hydrocortisone versus combination chemotherapy seems warranted in the premenopausal ER+ patient.

For postmenopausal ER+ patients, the ovarian source of estrogen is virtually nonexistent. Either antiestrogens or aminoglutethimide and hydrocortisone would be effective in countering any adrenal estrogen precursor production or action. Since chemotherapy has not been shown to be of benefit in this group, a placebo control arm is justified.

It should be emphasized that this scheme for future adjuvant trials is tentative at pres-

TABLE I. ER AND THE PROGNOSIS FOR EARLY RECURRENCE OF BREAST CANCER[a]

Category		Percentage recurrence at 18 months	
		ER−	ER+
Age	<50	34	14
	>50	35	8
Nodes	0	12	6.5
	1-3	38	12.5
	≥4	62	27.0
Size	<2 cm	33	0
	>2 cm	31	14

[a] Adapted from Ref. (9).

TABLE II. A SCHEME FOR AN ADJUVANT THERAPY TRIAL IN AXILLARY NODE-POSITIVE BREAST CANCER PATIENTS BASED ON ER STATUS

ER status	Menopausal status	Plan
ER−	Premenopausal	Chemotherapy A vs chemotherapy B
	Postmenopausal	Chemotherapy A vs placebo
ER+	Premenopausal	Ovariectomy + (antiestrogen or medical adrenalectomy) vs chemotherapy A
	Postmenopausal	Antiestrogen or medical adrenalectomy vs placebo

ent. There are currently many adjuvant trials underway which hopefully will provide new information to refine our thinking. On the other hand, most current trials have not taken ER stratification into account which may blunt the interpretation of the results.

Cytoplasmic receptor in advanced breast cancer. The measurement and use of cytoplasmic ER in deciding treatment strategy for patients wiith advanced breast cancer requires little discussion. It has taken much of the empiricism out of the decision-making process of whether to use or reject endocrine therapy in a particular patient. What is relatively new is that the response rate to endocrine therapy is proportionate to the actual quantitative amount of ER in the tumor specimen (4, 15). This is illustrated in Table III. Patients with very low amounts of ER respond infrequently whereas patients with very high levels of ER have very high response rates and intermediate ER values yield intermediate response rates. What therapy should we recommend based on quantitative ER values? In the case of low values the choice of chemotherapy is obvious since endocrine therapy will not be effective. In the intermediate group, the response rate to endocrine therapy is not sufficiently high to be dogmatic. Many of these patients will have good objective remissions to endocrine therapy. It would seem that a trial of endocrine therapy, preferably not major ablative surgery, is indicated with the plan to initiate chemotherapy if progression is observed. Alternatively, the simultaneous use of endocrine therapy and chemotherapy might be very effective. In the group with very high ER values, endocrine therapy alone is probably indicated in view of the very high response rates, reserving chemotherapy for subsequent progression. It is with this latter group that major ablative endocrine surgery could be considered since the associated morbidity may be justified.

Progesterone receptors and response to therapy in advanced breast cancer. In view of the success of ER to help select or reject endocrine therapy in patients with advanced breast cancer, many investigators have reasoned that the measurement of other receptors might even strengthen the correlations with endocrine therapy. We chose progesterone receptor (PgR) since in normal reproductive tissue the synthesis of PgR is dependent on estrogen stimulation (8). We were able to show that PgR could be measured in human breast tumor cytosols (17) and that PgR synthesis is stimulated by the direct addition of estradiol to human breast cancer cells in culture (6).

TABLE III. ER LEVEL IN METASTATIC BIOPSY AND RESPONSE TO ENDOCRINE THERAPY

ER value[a]	Response
<3	2/33 = 6%
3–10	24/52 = 46%
11–1000	21/26 = 81%

[a] fmole/mg cytosol protein; adapted from Ref. (15).

Numerous laboratories are now accumulating data on the correlation of ER and PgR and the response to endocrine therapies. A listing of all published data and personal communications is shown in Table IV. Since patient selection, assay methods, and criteria for objective response are probably different in each series, it is not legitimate to pool the data as in Table IV to arrive at definite conclusions. On the other hand, it is useful to illustrate the early results from a variety of centers. Several points are worth noting. First, the response rate of 14% in ER−, PgR- patients is high if one considers the response rates reported for ER alone in the past, but is best explained by the unusual results from one group in the series. Second, the presence of both receptors in a tumor specimen is associated with the highest response rates. Since we have previously shown that PgR is more likely to be present in tumors with high ER content (14), and that high ER content predicts for a higher response rate, it is not clear at this point whether PgR is just telling us that the ER content of the tumor is high and that a good response is to be expected, or rather that PgR is providing additional information independent of ER. This must be dealt with in future analyses. Now that ER and PgR data are beginning to appear from a variety of independent sources, we should in the very near future be able to conclude whether the measurement of PgR in addition to ER is of value.

Summary. The use of cytoplasmic estrogen receptor (ER) to help select patients with advanced breast cancer for endocrine therapy is well established and whenever possible should be part of the routine evaluation.

TABLE IV. OBJECTIVE RESPONSE TO ENDOCRINE THERAPY (231 CASES) BY RECEPTOR CONTENT

	ER−, PgR−	ER−, PgR+	ER+, PgR−	ER+, PgR+
McGuire *et al.*	0/11	—	7/17	13/16
Degenshein *et al.*[a]	0/7	1/1	1/9	16/18
King *et al.*[b]	1/5	1/2	1/7	8/9
Skinner *et al.*[c]	5/17	—	0/3	4/7
LeClercq *et al.* (11)	—	0/1	1/3	1/3
Matsumoto *et al.* (12)	2/20	0/1	9/25	12/20
Young *et al.* (21)	1/3	1/1	1/7	13/18
Total	9/63 = 14%	3/6	20/71 = 28%	67/91 = 74%

[a] Personal communication.
[b] King, R. J. B., Redgrave, S., Rubens, R. D., Millis, R., and Hayward, J. A., manuscript in preparation.
[c] Skinner, L. G., Barnes, D. M., and Ribeiro, G. G., manuscript in preparation.

Other potential uses of steroid receptors are emerging. The data suggest that an ER determination on the primary tumor may be very important in designing new adjuvant trials. Finally, the presence of progesterone receptor in a tumor signals the presence of a higher ER content and very likely a favorable response to endocrine therapy.

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