An Association between Steroid Hormone Receptors and Response to Cytotoxic Chemotherapy in Patients with Metastatic Breast Cancer

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Abstract

The relation between steroid hormone receptors and the response rate to cytotoxic chemotherapy in 70 patients with metastatic breast cancer was determined in a retrospective study. Thirty-four of 45 patients with low or absent estrogen receptor values had objective responses to chemotherapy, whereas only three of 25 patients with estrogen receptor-positive tumors responded (p < 0.0001). Furthermore, 22 of 34 patients with low or absent progesterone receptor tumors had an objective response to cytotoxic chemotherapy, while zero of eight patients with a positive progesterone receptor tumor responded (p < 0.01). Patients having tumors with a negative estrogen receptor and a negative progesterone receptor had a response rate of 21 of 24 (88%). This high response rate to chemotherapy in patients whose tumors lacked estrogen receptor or progesterone receptor could not be explained by differences between the two groups with respect to age, menopausal status, disease-free interval, Karnofsky performance index, sites of involvement with metastatic tumor, extent of disease, or type of chemotherapy administered.

Chemotherapy response was not associated with the presence or absence of either androgen or glucocorticoid receptor. We conclude that estrogen and progesterone receptor values are important predictors of response to cytotoxic chemotherapy in metastatic breast cancer.

Introduction

During the past decade a far greater understanding has evolved of the mechanism by which steroid hormones evoke specific phenotypic effects in target tissues. Perhaps the most critical advance has been provided by an appreciation that the initial step in steroid action is the binding of the hormone to specific intracellular receptor proteins. These hormone-receptor complexes are capable of interacting with chromatin and inducing qualitative and quantitative changes in transcriptional patterns of mRNA. Thus steroid receptors appear to be a necessary (if not sufficient) requirement for steroid hormone response. Based on this premise such receptors were sought and found in a variety of human cancers, and at least in the case of breast cancer, steroid hormone receptors play a major role in predicting response to endocrine manipulations. A large quantity of data has now been accumulated with regard to the estrogen receptor, and it has been unequivocally established that the estrogen receptor is useful in selecting patients for endocrine therapy. Patients whose tumors possess the estrogen receptor will respond to endocrine therapy 50 to 70% of the time while lack of the estrogen receptor is associated with a response rate of less than 10% (14). Furthermore, it has been suggested that the presence of both the estrogen receptor and the progesterone receptor in a tumor will further increase the response rate to classical endocrine therapy (13). Many human breast cancers also possess an androgen receptor (1, 7, 9, 16, 18), and both androgens and antiandrogens are effective endocrine therapies in some breast cancer patients (5). A specific glucocorticoid receptor is found in many normal human tissues, in blast cells in acute lymphoblastic leukemia (10), and in over 50% of human breast cancer specimens (1). Pharmacological doses of glucocorticoids play a role in the therapy of breast cancer (18) and also represent an important treatment modality in acute lymphoblastic leukemia (6). This "traditional role" for steroid hormone receptors in predicting response to endocrine therapy has been reviewed extensively (5, 6, 10, 13, 14, 16, 17). This chapter will deal with a new role for steroid hormone receptors, predicting response to cytotoxic chemotherapy.

The idea that the cytoplasmic receptor assays might be aid in predicting response to chemotherapy is based on the postulate that lack of one or more steroid hormone receptors might be correlated with a more rapid growth rate in a poorly differentiated tumor. These more rapidly growing tumors might be more sensitive to chemotherapy when compared to tumors that possess steroid hormone receptors. Recent evidence has shown that breast cancer tumors without estrogen receptor have a higher growth rate as measured by thymidine-labeling index and mitotic index (15), and it was felt that a correlation between this higher growth rate and chemotherapy response might exist. Patients whose primary breast cancer contains estrogen receptor have a prolonged disease-free survival when compared with receptor-negative tumors independent of menopausal status or involvement of the axillary lymph nodes by tumor (8). Furthermore, Knight et al. (18) have postulated that the lower frequency of estrogen receptor positivity in premenopausal women may account for their superior survival in adjuvant breast cancer therapy as opposed to postmenopausal patients. This postulate implies that the higher frequency of estrogen receptor negativity in premenopausal patients might be associated with greater sensitiv-
ity to chemotherapy. For these reasons we examined the effect of steroid hormone receptor status on response to cytotoxic chemotherapy.

Methods

Over the past 3 years, we have studied 70 patients who had one or more steroid hormone receptor assays performed immediately prior to a chemotherapy trial. Steroid hormone receptor assays were performed as previously described (11, 12). The cytoplasmic receptor protein is assayed with the dextran-coated charcoal technique under nonexchange conditions, that is, at a temperature (4°C) that does not allow for dissociation of endogenously bound, unlabeled estrogen during the time course of the assay. A positive estrogen, androgen, or glucocorticoid receptor assay was defined as equal to or greater than 10 fmol of [3H]estradiol, dihydrotestosterone, or dexamethasone binding per mg of cytoplasmic protein. A progesterone receptor assay was termed positive if it was equal to or greater than 20 fmol of [3H]R5020 binding per mg of cytoplasmic protein.

The 70 patients with metastatic or surgically unresectable primary breast cancer had one or more steroid hormone receptor assays performed immediately prior to the institution of a cytotoxic chemotherapy regimen. Generally speaking, the selection of patients for a chemotherapy trial as opposed to an endocrine manipulation was not done as a result of the steroid hormone receptor assay. In all cases, assessment of response was performed with standardized response criteria (3). In brief, complete response required the disappearance of all measurable disease including healing of all bone lesions and a return of the patient to a premorbid performance status. Partial response required a shrinkage of at least 50% in all measurable disease. Although a given lesion might not regress to this extent, regression averaged over all lesions had to be equal to or greater than 50%. No new lesions could appear, and no growth could be observed in a preexistent lesion. For purposes of this study, no patient was classified as a partial response unless improvement was maintained for 2 months or more. Objective response rate is the sum of complete plus partial responders. Any patient not achieving this degree of improvement was termed a nonresponder. Response to therapy was assessed by individuals unaware of the hormone receptor data.

Results

Estrogen Receptor. The characteristics of these patients (which have been previously published) are shown in Table 1. Of the 70 patients who had an estrogen receptor assay performed on their tumors, 45 were estrogen receptor negative and 25 were estrogen receptor positive. The 2 groups are virtually identical with regard to age, menopausal status, Karnofsky performance index, disease-free interval, number of sites involved with metastatic tumor, and prior therapy. The distribution of treatments received by both groups was also very similar, with 64% of the estrogen receptor-positive patients receiving combination chemotherapy consisting of Adriamycin plus one or more other chemotherapeutic agents compared to 71% in the estrogen receptor-negative group. The specific therapies used are listed in Table 2.

Thirty-four of 45 estrogen receptor-negative patients treated with cytotoxic chemotherapy achieved an objective response compared to 3 of 25 in the estrogen receptor-positive group (p < 0.0001). Chart 1 illustrates the distribution of estrogen receptor values as a function of objective response. At this time we are unable to define with certainty as estrogen receptor value cutoff for chemotherapy response that is more helpful than the one chosen arbitrarily. Even without regard to the cutoff value of positivity, the distribution of fmol/mg cytoplasmic protein for responders differs significantly from the corresponding distribution for nonresponders (p < 0.0005).

The only major difference between the 2 groups that we were able to identify concerned sites of involvement with metastatic tumor. Seventy-six percent of the estrogen receptor-positive group had visceral (lung and liver) involvement by metastatic tumor compared to 44% in the estrogen receptor-negative group. Because of this difference, which might tend to give the estrogen receptor-positive group a poorer response rate, we analyzed our response data as a function of the presence or absence of visceral tumor involvement. This is illustrated in Table 3. As shown, regardless of whether or not visceral involvement was documented, patients whose tumors lack estrogen receptor had a much higher response rate to chemotherapy. Patients whose

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Table 1

<table>
<thead>
<tr>
<th>Estrogen receptor</th>
<th>Positive</th>
<th>Negative</th>
<th>p ER+ vs. ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Mean estrogen receptor (fmol/mg cytoplasmic protein)</td>
<td>56</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50 ± 10a</td>
<td>52 ± 11</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>6/25 (24)</td>
<td>13/45 (28)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>19/25 (76)</td>
<td>32/45 (72)</td>
<td></td>
</tr>
<tr>
<td>Karnofsky index</td>
<td>89 ± 10</td>
<td>88 ± 10</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Disease-free interval (mos.)</td>
<td>17 ± 11</td>
<td>22 ± 12</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>No. of sites involved</td>
<td>1</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>7/25 (28)</td>
<td>9/45 (20)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Endocrine</td>
<td>7/25 (28)</td>
<td>9/45 (20)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1/25 (4)</td>
<td>1/45 (2)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Median time from first recurrence to chemotherapy trial (mos.)</td>
<td>1.5</td>
<td>3.0</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

a Mean ± S.D.
b Numbers in parentheses, percentage.
tumors were estrogen receptor negative and who had visceral involvement with metastatic tumor had an objective response rate of 10 of 20 (50%). Those without visceral tumor involvement had a remarkably high response rate of 24 of 25 (96%).

The effect of number of sites involved on response rate as a function of receptor status is shown in Table 4. As shown, response rates are significantly higher for estrogen receptor-negative patients when adjusted for number of sites of involvement than for receptor-positive patients.

The most important confirmation of the accuracy of the estrogen receptor assay derives from our correlations of estrogen receptor to endocrine therapy. In 85 other patients, 34 of 52 (65%) who were estrogen receptor positive responded to endocrine therapy whereas 3 of 33 (9%) estrogen receptor-negative patients responded to endocrine manipulation (p < 0.0001). These results are similar to those previously reported by many groups (14) and provide confidence that our assay methodology and patient assessment criteria are reliable.

**Progesterone Receptor.** Forty-two patients had a progesterone receptor assay performed on their tumors. Eight were progesterone receptor positive, and 34 were receptor negative. The characteristics of these 2 groups are listed in Table 5. The 2 groups of patients whose tumors are either progesterone receptor positive or negative are essentially identical with respect to age, menopausal status, Karnofsky performance index, disease-free interval, number of sites involved with metastatic disease, and proportion of patients with visceral involvement. Three of 8 (38%) of the patients in the progesterone receptor-positive group had received prior endocrine or chemotherapy compared to 4 of 34 (12%) in the receptor-negative group. This difference is not statistically significant. The chemotherapy received by the 2...
groups was similar. The distribution of the progesterone receptor as a function of response to cytotoxic chemotherapy is shown in Chart 2. Zero of 8 patients whose tumors contained progesterone receptor responded objectively to chemotherapy, whereas 22 of 34 (64%) whose tumors lacked progesterone receptor responded \( p < 0.05 \). Even without regard to the cutoff value of positivity for the progesterone receptor, the distribution of progesterone receptor values expressed as fmol/mg cytoplasmic protein for responders differs significantly from the corresponding distribution for nonresponders \( p < 0.05 \).

Objective response rate to chemotherapy as a function of both the estrogen and progesterone receptors is shown in Table 6. The response rate in patients who are estrogen receptor positive is very small. This response rate does not change as a function of the presence or absence of a progesterone receptor. Progesterone receptor, however, does appear to affect the response rate of the patients whose tumors lack estrogen receptor. Patients who are estrogen and progesterone receptor negative have a response rate of 21 of 24 (88%). Unfortunately, there are only 3 patients who are estrogen receptor negative but progesterone receptor positive. None of these patients responded, but the group is too small to perform a meaningful statistical test.

**Androgen Receptor.** Forty-three patients had an androgen receptor assay performed on their tumors. Eleven were androgen receptor positive, and 32 lacked the androgen receptor. Five of 11 (45%) patients whose tumors were androgen receptor positive had an objective response to chemotherapy, and 16 of 32 (50%) patients whose tumors had negative androgen receptor responded \( p > 0.1 \). The distribution of androgen receptor values expressed as fmol/mg cytoplasmic protein does not differ between the responders and nonresponders. The response rate to cytotoxic chemotherapy as a function of both the estrogen and androgen receptors is shown in Table 7. The presence or absence of an androgen receptor does not alter the response rate in patients whose tumors are estrogen receptor negative. No differences between the androgen receptor-positive and -negative groups with regard to age, menopausal status, Karnofsky performance index, disease-free interval, or extent of disease could be identified that could explain why androgen receptor did not correlate with response to cytotoxic chemotherapy.
Table 8
Objective response rate to cytotoxic chemotherapy as a function of estrogen and glucocorticoid receptor status

<table>
<thead>
<tr>
<th>Receptor status</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen receptor positive</td>
<td>Glucocorticoid receptor positive</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoid receptor negative</td>
</tr>
<tr>
<td>Estrogen receptor negative</td>
<td>Glucocorticoid receptor positive</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoid receptor negative</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage.

**Glucocorticoid Receptor.** Thirty-nine patients had a glucocorticoid receptor assay performed on their tumors. Thirty-one were glucocorticoid receptor positive, and 8 were glucocorticoid receptor negative. Fourteen of 31 (45%) patients whose tumors were glucocorticoid receptor positive responded to chemotherapy while 5 of 8 (62%) whose tumors lacked glucocorticoid receptor responded (p > 0.1). The distribution of glucocorticoid receptor values expressed as fmol/mg cytoplasmic protein does not differ between the responders and nonresponders. The response rate to chemotherapy as a function of both the estrogen and glucocorticoid receptor is shown in Table 8. The presence or absence of a glucocorticoid receptor does not alter the response rate in patients whose tumors are either estrogen receptor positive or negative. No differences between the glucocorticoid receptor-positive and -negative groups with regard to age, menopausal status, Karnofsky performance index, disease-free interval, or extent of disease could be identified, which explained why glucocorticoid receptor did not correlate with response to cytotoxic chemotherapy.

**Discussion and Conclusions**

Data have been presented correlating lack of estrogen and progesterone receptors with an increased response rate to cytotoxic chemotherapy. This correlation is a new role for the estrogen and progesterone receptors in addition to their more traditional role of predicting response to endocrine therapy. This association between lack of estrogen and progesterone receptors and chemotherapy response has many implications with regard to the treatment of breast cancer.

The first area in which our data may have some influence is adjuvant therapy. The benefit of adjuvant therapy in premenopausal patients with breast cancer is now established; however, no benefit has been demonstrated for postmenopausal patients (2, 4). We feel that since a larger proportion of the premenopausal patients lacks the estrogen receptor in their tumors, estrogen receptor negativity may translate into greater sensitivity to chemotherapy and hence more benefit from adjuvant chemotherapy. The postmenopausal patients are a group whose tumors possess estrogen receptor with higher frequency. These estrogen receptor-positive tumors may be more differentiated than their estrogen receptor-negative counterparts and hence may have a slower growth rate and be less sensitive to cytotoxic chemotherapy. If our preliminary results are confirmed by other investigators, it would seem reasonable to stratify patients in adjuvant chemotherapy trials according to estrogen receptor status. Also, in an attempt to benefit postmenopausal patients, a therapeutic regimen could be designed that combined both cytotoxic chemotherapy and endocrine therapy.

The second area in which our results may have some impact is in the design of cytotoxic chemotherapy trials. The concept of the randomized prospective study is well established, and it has a known potential for decreasing study bias in terms of patient selection. Even in a randomized trial, if certain aspects are identified that are known to influence response, then the patients should be stratified according to these factors. Examples would include the nodal status stratification in the adjuvant chemotherapy trials or stratification by Karnofsky performance index in trials of cytotoxic chemotherapy in metastatic breast cancer. We feel that if our response data are validated then it would be logical to stratify all patients with metastatic breast cancer in cytotoxic chemotherapy trials by their estrogen receptor status. In this manner another possible study bias would be eliminated. Our data also point out once again the pitfalls of the use of “historically matched controls” since it is impossible to match groups by factors not yet identified.

Finally, the lack of response of the steroid hormone receptor-positive tumors is interesting. At this time we do not know why they fail to respond to cytotoxic chemotherapy. It may be that the presence of the estrogen receptor in a tumor cell is related to cellular differentiation and decreased growth rate and hence is associated with a diminished sensitivity to cytotoxic chemotherapy. If these postulates are true, then the oncologist is faced with both an interesting and challenging problem, that is, to devise some mechanism to make these tumors sensitive to chemotherapy. One possible therapeutic design would be to attempt to arrest positive cells in a uniform stage of the cell cycle with antiestrogen therapy. This could then be followed by estrogen administration resulting in a parasynchronous wave of cells in the S phase of the cell cycle that might then be killed by S-phase-specific cytotoxic chemotherapy. This type of study is currently in progress at the National Cancer Institute.

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