

PROGESTERONE RECEPTORS AS A PROGNOSTIC FACTOR IN STAGE II BREAST CANCER

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Abstract The presence of estrogen receptors in breast cancers is now accepted as a predictor of extended disease-free survival, but the relative value of progesterone receptors for this purpose has not been established. We have examined both receptors along with other risk factors in 189 patients receiving adjuvant therapy for Stage II breast cancer. The presence of either estrogen receptors or progesterone receptors was positively correlated with disease-free survival when analyzed separately, whether or not the adjuvant regimen included an endocrine component. However, when estrogen receptors and progester-

one receptors were analyzed together in multivariate models, the presence of progesterone receptors was more significant than that of estrogen receptors for predicting time to recurrence, regardless of what other variables were included in the model. These data suggest that determination of the progesterone-receptor concentration is of equal or greater value than determination of the estrogen-receptor concentration for predicting the disease-free survival of patients with breast cancer. Future trials should include measurement of progesterone receptors. (N Engl J Med 1983; 309:1343-7.)

IN 1974 a study of adjuvant treatment of Stage II breast cancer was initiated. Patients were initially stratified according to the presence or absence of estrogen receptors in their primary tumor. Patients with tumors that were positive for estrogen receptors have had delayed recurrence and longer survival than patients whose tumors were negative, regardless of their treatment.¹⁻⁴

In 1975 Horwitz et al. hypothesized that the presence of progesterone receptors in human breast tumors might be a sensitive marker for predicting the response to endocrine therapy.⁵ Subsequent clinical correlations in small groups of patients showed that tumors containing progesterone receptors regressed much more frequently after endocrine treatment than tumors without these receptors.⁶ A corollary to this hypothesis is that the presence of progesterone receptors may be an important predictor of time to recurrence for patients who receive adjuvant endocrine therapy for primary breast cancer.

Although progesterone-receptor status was not considered in the original design of the study of adjuvant therapy, progesterone-receptor levels were routinely measured in specimens sent to our laboratory in San Antonio for estrogen-receptor analysis. This report presents a new analysis of this study, examining the progesterone receptor as a potential factor for predicting disease-free survival in breast cancer.

METHODS

The patients, methods of stratification and randomization, and treatment regimens for the study of adjuvant therapy have been described in detail elsewhere.¹⁻⁴ In brief, between September 1974 and June 1979, 318 women with Stage II breast cancer (i.e., positive axillary lymph nodes) underwent radical or modified radical mastectomies and were entered in this clinical trial. Estrogen-receptor assays were performed in specimens from the primary tumor of each

patient. The patients were stratified according to estrogen-receptor status and number of positive axillary nodes (one to three vs. more than three). Within each stratum, patients were randomly assigned to one of three treatment combinations: cyclophosphamide, methotrexate, and fluorouracil (CMF); CMF plus tamoxifen; or CMF plus tamoxifen plus bacille Calmette-Guérin vaccine. Physical examinations and blood chemistry studies were performed at three-month intervals. Routine chest films were taken at six-month intervals, and bone scans and mammograms at yearly intervals. The end point of the study was the first documented recurrence.

Since measurement of progesterone-receptor levels was not included in the original study design, we were able to analyze only a subset of the study patients. We elected to study only the patients whose assays were performed in a single laboratory. Of the original 318 patients, 7 were eliminated because of initial protocol infringements, leaving 311 patients followed since inception of the study. Estrogen-receptor levels were measured in San Antonio for 210 of these patients. Progesterone-receptor levels were also measured in 189 of these patients (61 per cent of those evaluable).

Steroid Receptors

The methods for the steroid-receptor assays performed in San Antonio have been described previously.^{7,8} Estrogen-receptor concentrations were measured by the dextran-coated charcoal technique, and progesterone-receptor levels by the sucrose-density-gradient method. Specimens were considered estrogen-receptor positive if they contained at least 3 fmol of specific binding sites per milligram of protein and progesterone-receptor positive if they contained at least 5 fmol per milligram of protein.

Statistical Methods

Disease-free survival curves were calculated by the method of Kaplan and Meier.⁹ Tests of differences between curves were made with the log-rank test for censored survival data.¹⁰ Cox's partially nonparametric regression model was used to evaluate the predictive power of various combinations and interactions of prognostic factors in a multivariate manner.¹¹⁻¹³ The patient characteristics included in the models were levels of the estrogen and progesterone receptors, the number of positive axillary lymph nodes, the size of the primary tumor, menopausal status, and treatment regimen. The steroid receptors were analyzed as both qualitative (i.e., positive vs. negative) and quantitative factors. Because the distributions of these receptor levels were known to be highly skewed, the quantitative values were expressed as logarithms of the receptor concentrations. All computations were performed with the Biomedical Computer Programs — P Series, 1981.¹⁴

RESULTS

Patients who had progesterone-receptor assays performed in San Antonio were compared with those who did not; in order to evaluate possible selection bias

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Table 1. Characteristics of Patients with and without Progesterone-Receptor (PgR) Assays.

| VARIABLE | P VALUE | PATIENTS WITH PgR ASSAYS (n = 189) | PATIENTS WITHOUT PgR ASSAYS (n = 122) |
|--------------------------------|---------|------------------------------------|---------------------------------------|
| Menopausal status | 0.48 | | |
| Pre or peri | | 73 (39%) | 44 (36%) |
| Post | | 116 (61%) | 78 (64%) |
| No. of positive nodes | 0.77 | | |
| 1-3 | | 90 (48%) | 56 (46%) |
| >3 | | 99 (52%) | 66 (54%) |
| Size of primary tumor | 0.22 | | |
| ≤2 cm | | 38 (20%) | 18 (15%) |
| >2 cm | | 150 (80%) | 104 (85%) |
| Treatment * | 0.36 | | |
| CMF | | 64 (34%) | 37 (30%) |
| CMF+T | | 61 (32%) | 49 (40%) |
| CMF+T+BCG | | 64 (34%) | 36 (30%) |
| Estrogen-receptor level | 0.54 | | |
| <3 fmol/mg (ER-) | | 45 (24%) | 33 (27%) |
| ≥3 fmol/mg (ER+) | | 144 (76%) | 89 (73%) |
| Median estrogen-receptor level | 0.45 | 21 fmol/mg | 25 fmol/mg |
| Median follow-up | | | |
| All patients | 0.17 | 32 mo | 37 mo |
| Disease-free patients | 0.41 | 41 mo | 43 mo |
| Disease-free survival | 0.05 | | |
| 90th percentile | | 14 mo | 17 mo |
| 75th percentile | | 24 mo | 32 mo |

*CMF denotes cyclophosphamide, methotrexate, and fluorouracil, CMF+T denotes CMF plus tamoxifen, and BCG denotes bacille Calmette-Guérin vaccine.

in this subset of patients. Percentages were compared by chi-square analysis; estrogen-receptor levels and follow-up times were compared by Wilcoxon rank-sum tests. There were no significant differences in any of the demographic characteristics, treatment assignment, or follow-up times between patients who had progesterone-receptor levels measured in San Antonio and those who did not (Table 1). However, the overall disease-free interval was significantly shorter ($P = 0.05$) in patients for whom progesterone-receptor information was available. This finding was surprising, especially in the light of the lack of differences in any of the usual risk factors, including tumor size. One possible explanation could be institutional differences. The patients in this study were treated at 10 different institutions, 5 of which routinely sent biopsy specimens to San Antonio. The other five institutions used other laboratories for analyses of steroid receptors.

Table 2 shows the results of the disease-free survival analyses for the 189 patients with progesterone-receptor measurements when the prognostic factors were considered one at a time. The number of positive axillary nodes and the size of the primary tumor were each negatively correlated with time to recurrence. That is, patients with many positive nodes or large tumors had shorter disease-free intervals. Both estrogen receptors and progesterone receptors were positively correlated with time to recurrence, whether expressed as qualitative or quantitative factors. There were no overall significant differences in disease-free survival between premenopausal and postmenopausal women or

among the treatment regimens. Since there was no significant difference in disease-free survival distributions between the CMF plus tamoxifen treatment regimens with and without bacille Calmette-Guérin vaccine ($P = 0.74$), these two groups were combined. Even then the effect of including tamoxifen in the regimen was not significant.

We next examined the relations between the steroid-receptor levels and disease-free intervals in more detail. The finding that the qualitative expressions of both estrogen-receptor and progesterone-receptor levels were highly correlated with disease-free survival indicated that patients with high levels of these receptors should have a longer time to recurrence. Figure 1 shows that this was the case for the progesterone receptor. Patients with low receptor levels had significantly shorter disease-free survival than did patients with moderate levels; patients with high progesterone-receptor levels fared significantly better than patients with moderate levels. However, the relation was not as strong for the estrogen receptor. Figure 2 confirms that patients with low estrogen-receptor levels had recurrences sooner than patients with moderate levels. However, there was no significant difference between patients with high estrogen-receptor levels and those with moderate levels.

The association between the estrogen receptor (ER) and the progesterone receptor (PgR) was examined by dividing the patients into four groups according to the presence or absence of the two receptors: (1) ER+/PgR+, (2) ER+/PgR-, (3) ER-/PgR+, and (4) ER-/PgR-. (The third group comprised only six patients and was not further analyzed.) Disease-free survival was significantly better for the ER+/PgR+ group than for either the ER+/PgR- or ER-/PgR- group ($P = 0.03$ and $P < 0.0001$, respectively; Fig. 3). However, the disease-free survival of the ER+/PgR- group was only marginally better than that of the ER-/PgR- group ($P = 0.06$). Even though the sample sizes in these groups were relatively small, these results suggest that the presence of the progesterone receptor may be more important than the presence of the estrogen receptor.

Table 2. Results of Univariate Disease-Free-Survival Analyses.

| VARIABLE | P VALUE |
|---|--------------------|
| No. of positive nodes (1-3 vs. >3) | <0.0001 |
| Size of primary tumor (≤2 cm vs. >2 cm) | 0.0062 |
| Progesterone receptor (Logarithm) (<5 fmol vs. ≥5 fmol) | <0.0001 <0.0001 |
| Estrogen receptor (Logarithm) (<3 fmol vs. ≥3 fmol) | 0.0013 0.0008 |
| Menopausal status (pre or peri vs. post) | 0.4592 |
| Treatment * (CMF vs. CMF+T) | 0.5696 |

*Defined in footnote to Table 1.

An obvious disadvantage of analyzing prognostic factors one at a time is that interactions between factors cannot be examined. When two or more variables are combined into subgroups (e.g., ER+/PgR+, ER+/PgR-, and ER-/PgR-), the sample sizes within the various subgroups become small. One solution is to use a multivariate model, which can incorporate several prognostic variables and their interactions simultaneously. The result obtained with these procedures is a set of regression coefficients corresponding to the prognostic factors in the model. If a particular prognostic factor is deemed statistically significant, the implication is that if all other variables in the model are held constant, then a change in the value of the factor in question will significantly affect disease-free survival.

We examined several subsets of variables with Cox's multiple regression technique. Both untrans-

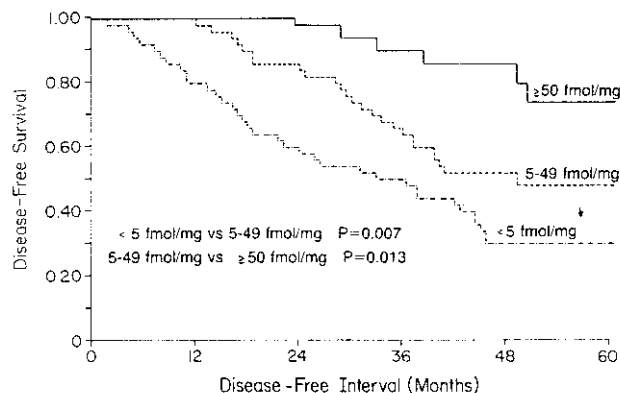


Figure 1. Disease-Free Survival Curves Compared with Progesterone-Receptor Levels.

Disease-free survival was related to the amount of progesterone receptor. Patients with at least 50 fmol per milligram of protein (n = 80) had significantly longer disease-free survival than patients with 5 to 49 fmol per milligram of protein (n = 68); each of these groups had longer disease-free periods than patients with less than 5 fmol per milligram of protein (n = 41).

formed and transformed factors as well as all pairwise interactions were investigated. Table 3 shows the results of the analysis including the number of positive nodes, the size of the primary tumor, both steroid receptors expressed as quantitative factors, menopausal status, and treatment regimen. Consistent with the univariate analyses, both the number of positive nodes and the level of the progesterone receptor were significant prognostic factors (P<0.0001), whereas the size of the primary tumor was of only borderline significance (P = 0.11).

The surprising result was the lack of significance of the estrogen-receptor level either as a single variable or as an interaction with any of the other variables. The results were identical when estrogen-receptor status was expressed as positive or negative, with only minor changes in the P values for the factors not in the model. That is, if the number of positive nodes, the progesterone-receptor content, the size of the primary tumor, and the menopausal status were known, then

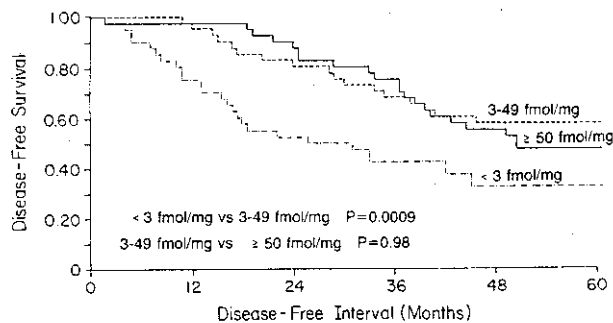


Figure 2. Disease-Free Survival Curves Compared with Estrogen-Receptor Levels.

Patients with estrogen-receptor levels below 3 fmol per milligram of protein (n = 45) had significantly shorter disease-free survival than did patients with moderate or high levels. However, there was no difference in disease-free interval between patients with 3 to 49 fmol per milligram of protein (n = 82) and those with higher levels (n = 62).

the estrogen-receptor level did not provide any additional prognostic power for predicting disease-free survival.

A number of other combinations were examined in the same way. As long as the estrogen and progesterone receptors were considered simultaneously, estrogen-receptor levels never enhanced the prediction of recurrence, no matter what other variables were included in the model. On the other hand, progesterone-receptor status and the number of positive nodes always remained significant prognostic factors, suggesting that the additional knowledge of the progesterone-receptor level will help predict disease-free survival, even if estrogen-receptor status is already known.

DISCUSSION

The primary objective of our original study was to investigate various methods of adjuvant treatment of

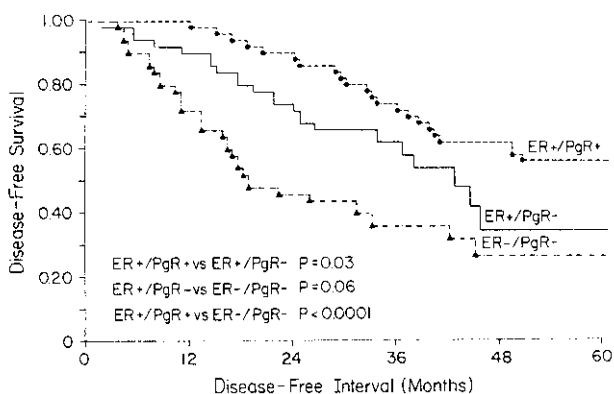


Figure 3. Disease-Free Survival Curves Compared with Estrogen-Receptor and Progesterone-Receptor Status.

Patients who were estrogen-receptor positive (ER+) and progesterone-receptor positive (PgR+) (n = 104) had significantly longer disease-free survival than patients who had estrogen receptors but lacked progesterone receptors (n = 39), or patients who lacked both receptors (n = 40). However, among patients who lacked progesterone receptors, disease-free survival was only marginally longer for those who had estrogen receptors than for those who lacked estrogen receptors.

Table 3. Results of Multivariate Disease-Free Survival Analyses.

| VARIABLE | P VALUE |
|--|---------|
| In the model | |
| Positive nodes (1-3 vs. >3) | <0.0001 |
| Progesterone receptor (logarithm) | <0.0001 |
| Not in the model * | |
| Size (≤ 2 cm vs. > 2 cm) | 0.11 |
| Estrogen receptor (logarithm) | 0.26 |
| Treatment (CMF vs. CMF+T) | 0.56 |
| Menopausal status (pre or peri vs. post) | 0.94 |

*None of the pairwise interactions was significant.

Stage II breast cancer. The focus of the present analysis was to determine the relation between the progesterone receptor and disease-free survival. The progesterone receptor was a significant predictor of disease-free survival in the group of patients analyzed. However, the median follow-up at the time of analysis was still quite short for this particular disease. Continued follow-up will be necessary to make sure that the correlations that have been observed do not lessen with time.

The progesterone receptor has been considered by other investigators. Saez et al. examined the prognostic value of the estrogen and progesterone receptors in patients with resectable breast cancer.¹⁵ The recurrence rate for patients with both receptors was significantly lower than the rate for patients who lacked these receptors. However, this study did include node-negative patients. Pichon and colleagues investigated the relation between the progesterone receptor and prognosis in a small group of patients in various early stages of breast cancer.¹⁶ Overall, they concluded that the presence of the progesterone receptor in primary tumors was associated with a markedly lower frequency of metastases. These results are in accordance with those of Bertuzzi et al., who reported that the progesterone receptor was a better indicator of recurrence than the estrogen receptor in patients with negative nodes.¹⁷ On the other hand, Allegra et al. did not find an association between the progesterone receptor and the disease-free period.¹⁸ However, over one third of the patients in their study had biopsy specimens of metastatic lesions rather than primary tumors. Once these patients were excluded, the sample sizes may have been too small to reveal significant differences.

There is a good rationale for the relation between progesterone-receptor levels and disease-free survival. The synthesis of the progesterone receptor is dependent on estrogen stimulation in normal reproductive tissues and in human breast-cancer cell lines in culture.^{5,6} Since it has been well documented that the presence of the estrogen receptor is predictive of improved survival and longer disease-free periods,¹⁹ it is possible that patients who have progesterone receptors comprise a group with a better prognosis. However, absence of the progesterone receptor may be due to nonfunctional estrogen receptor or simply to the absence of estrogen. In this study, only estrogen-receptor

levels, not estrogen levels, were measured.

Disease-free survival was directly related to the amount of progesterone receptor in the tumor. Time to recurrence was also related to estrogen-receptor content, but high levels of this receptor did not provide an advantage over moderate levels. The number of positive axillary lymph nodes was the single most important predictor of disease-free survival. This is well known and is precisely why the study design required stratification on the basis of this variable in 1974. The prognostic value of menopausal status has been a subject of much debate in several studies, and menopausal status was significant in this study only through its interaction with the size of the primary tumor. Tumor size was an important prognostic factor when considered alone but lost statistical significance when considered simultaneously with other factors. The treatment effects in this study have been extensively analyzed and presented previously.¹⁻⁴ With long-term follow-up of the full group, patients with estrogen receptors who are receiving tamoxifen continue to have a better outcome. In the present subgroup of patients, there was no significant advantage for tamoxifen-treated patients, perhaps because of the decreased sample sizes. It should be emphasized that all patients in this study received adjuvant chemotherapy, which, with or without tamoxifen, may act partly through a hormone-ablative mechanism. This could help explain the lack of significant differences for the tamoxifen-containing regimens among these patients, but other considerations, such as the short period of treatment with tamoxifen (one year), are more plausible.

Conclusions regarding a lack of significance of prognostic factors should not be made without considerable caution. The estrogen receptor was not a significant prognostic factor in the multivariate models we examined. Even though the P values for the estrogen receptor and each of its interactions exceeded 0.25, it may not be safe to conclude that the presence of this receptor provides absolutely no additional prognostic information. However, we feel reasonably secure in concluding that the progesterone receptor is more important than the estrogen receptor for predicting disease-free survival.

The presence of progesterone receptors was a significant prognostic factor for time to recurrence, whether it was considered as a single variable or in combination with any of the other variables that were analyzed. Thus, progesterone-receptor levels should be routinely measured and incorporated into future trials of adjuvant therapy.

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MARROW TRANSPLANTATION FOR ACUTE NONLYMPHOCYTIC LEUKEMIA AFTER TREATMENT WITH BUSULFAN AND CYCLOPHOSPHAMIDE

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Abstract Fifty-one patients with acute nonlymphocytic leukemia (16 with end-stage disease, 17 in second or third remission or in early relapse, and 18 in first remission) were given infusions of HLA-identical sibling marrow after cytoreduction with high doses of busulfan and cyclophosphamide. Actuarial two-year survival rates were 0 per cent, 29 per cent, and 44 per cent, respectively. Twelve patients are still alive and in remission after 327 to 1488 days, with 10 surviving beyond two years. Acute graft-versus-host disease and viral pneumonia were the major causes of death. Leukemic cells failed to clear in one patient with end-stage disease, and a relapse with menin-

geal leukemia occurred in another. Only one other relapse was seen — in a patient given a transplant during a third remission. Survival was favorably affected by younger age and transplantation during first remission. We conclude that high-dose chemotherapy with busulfan and cyclophosphamide, followed by allogeneic-marrow transplantation, can produce long-term remission of acute leukemia. Chemotherapy with high-dose busulfan and cyclophosphamide before transplantation provides an effective alternative to cyclophosphamide and total-body irradiation before transplantation for the treatment of acute nonlymphocytic leukemia. (*N Engl J Med* 1983; 309:1347-53.)

THE treatment of acute nonlymphocytic leukemia with high-dose chemotherapy and total-body irradiation followed by allogeneic bone-marrow transplantation has been attempted by a number of centers. Therapeutic results have been encouraging, especially when patients have received transplants during first remission. Long-term remissions and possible cure rates of 50 per cent or higher have been obtained.¹⁻⁵

We describe the use of high doses of busulfan and cyclophosphamide as preparation for bone-marrow transplantation in acute nonlymphocytic leukemia in three groups of patients: 16 patients in full relapse

considered to have refractory leukemia (Group I), 17 patients in second or third remission or in early relapse (Group II), and 18 patients given a transplant during first remission (Group III). In all cases genotypic HLA-identical allogeneic marrow from a sibling was infused after treatment with high doses of busulfan and cyclophosphamide.

METHODS

Informed Consent

All protocols were reviewed and approved by the Johns Hopkins University Institutional Review Board.

Patient Selection

To be eligible for these studies, patients had to have a diagnosis of acute nonlymphocytic leukemia confirmed by examination of a marrow aspirate. In addition, they had to have a negative history for central-nervous-system leukemia and a spinal fluid free of leukemic cells on cytocentrifuge examination. In patients undergoing transplantation during remission, the absence of leukemic cells was confirmed by marrow aspiration upon admission to our service. All patients referred to our service who met these criteria for eligibility

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