original research report

Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients

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BACKGROUND: This study was conducted to determine the prognostic effect hormone receptor (HR) status in early HER2 positive (HER2+) breast cancer patients, since it has not yet been established whether HR status can be used in the prognosis of patients with (HER2+) breast cancer.

PATIENTS AND METHODS: We obtained data from 299 patients with early HER2+ breast cancer who underwent surgery and received standard adjuvant chemotherapy, hormonal therapy and/or radiation between 2000 and 2002 at the Instituto Nacional de Enfermedades Neoplasicas, Perú. Clinical and pathological features were compared. Endpoints analyzed were disease free survival (DFS) and overall survival (OS).

RESULTS: Overall, 155 patients were HR-positive (HR+) and 144 were negative (HR-). The two groups had similar characteristics except for histologic grade and extracapsular extension. With a median follow-up of 93 months, 5-year DFS was statistically different between the two groups: 65.0% for (HER2+/ HR-) and 74.6% for the (HER2+/ HR+) patients (P=.045). OS at 5 years was not statistically different between the two groups with 75.5% for (HER2+/ HR-) patients and 82.4% for the (HER2+/ HR+)(P=.140).

CONCLUSIONS: Patients with (HER2+/ HR-) breast cancers treated with surgery and standard adjuvant chemotherapy exhibited a statistically worse DFS compared to those with (HER2+/ HR+) tumors. However, OS was similar in both groups.

Breast cancer is one of the most common malignancies affecting women worldwide. Despite the fact that early disease can be cured by surgery, at least 30% of patients develop disease recurrence, while only 40% of patients with node-positive disease are alive without disease recurrence at 10 years.[1] Prognostic factors, which include growth factors and oncogenes, not only help in assessing the overall prognosis, but also serve a crucial role in the treatment decision. Two of the most studied prognostic factors are hormone receptors (HR) and amplification of the human epidermal growth factor receptor 2 (*HER2*) oncogene. The latter is present in approximately 20% of cases, almost half of which also express HR. These factors are also predictive of response to systemic treatments, including targeted agents. Thus, in addition to the demonstrated benefit of adjuvant hormonal therapy, some recent randomized trials have shown a clinical benefit of adding trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of *HER2*, to chemotherapy in early breast cancer patients.[2-5]

Hormone and *HER2* receptor pathways are intimately related and a complex network between them has been demonstrated. A variety of in vitro and in vivo models have shown an inverse relationship between *HER2* overexpression and rates and duration of response to hormone modulation.[6-8] Additionally, an inverse relationship between positive staining for the estrogen receptor and *HER2* overexpression has been described.[5,9] Clinical evidence of the participation of the *HER2* pathway in endocrine resistance in the adjuvant breast cancer setting, is prognostically detrimental in patients with positive steroid receptor who overexpress *HER2*.[5,7,8] The clinical effect of the interaction of these factors in the prognosis of early breast cancer is not completely understood. It has not yet been established whether hormone receptor status can be used in the prognosis of patients with *HER2* positive (HER2+) breast cancer who have received standard adjuvant chemotherapy without trastuzumab, nor if the influence

of *HER2* in the sensitivity to hormonal therapy could change the treatment decision for some subsets of low risk breast cancer.[10,11] The aim of the present study was to evaluate the prognostic contribution of HR status in relation to *HER2* overexpression in breast cancer.

PATIENTS AND METHODS

We retrospectively analysed data from female patients with early (stage I- III) HER2+ breast cancer who underwent curative surgery followed by adjuvant treatment at the Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima, Peru, between 2000 and 2002. Patients also had to have complete clinical follow-up reported in their medical file and detailed pathology reports.

Accepted adjuvant treatments were chemotherapy, endocrine treatment and local radiation, all of which had to have been administered according to international guidelines and or local guidelines. No patients had received adjuvant trastuzumab, as at the time it was not a standard treatment choice. Follow-up after completion of adjuvant treatment usually involved a regular schedule of visits every 4 weeks initially, which was progressively extended to every 6 months, except for patients requiring more frequent visits. Patients had regular blood tests and image tests.

HER2 status was identified using currently applicable clinical methodology. The antibody anti-HER2/neu (A0485 Dako) was used to quantify immunohistochemical staining. All 3+ (high intensity) staining specimens were considered positive. All 2+ (moderate intensity) staining specimens underwent florescence in situ hybridization (FISH) analysis, and those that showed HER2 amplification were classified as positive. Estrogen and progesterone receptors (ER and PR) were evaluated by immunohistochemisty, and were considered positive if more than 10% of tumor cells were positively (weak or strong) stained.

Quantitative and qualitative variables were evaluated using mean and standard deviation, and proportions, respectively. Differences between the two hormone receptor subgroups ([HER2+/ HR–] versus [HER2+/ HR+]) were examined using analysis of variance (ANOVA) for age and tumor size, with a previous evaluation of the fulfilling of all, the assumption of normality, homogeneity of variance and independence. The chi-square test was used to evaluate the association between the different breast cancer subgroups and the principal clinical and pathological features of prognostic importance.

Disease free survival (DFS) was chosen as the primary end point and defined as the time from the primary surgery to the first recurrence, death or last follow-up in the case of patients without recurrence. Overall survival (OS) was calculated from the time of diagnosis to death or last follow-up. The survival curves were calculated using the Kaplan-Meier method.[12]

The log-rank test was used to determine the statistical significance of the differences observed between the groups of hormone receptors ([HER2+/ HR–] versus [HER2+/ HR+]). Multivariate Cox regression models were developed to obtain both relative risks (hazard ratio) and 95% confidence intervals (CIs) for the main clinical pathologic variables. The covariables included in this model were specific for age ranges, clinical stages, histological grade, menopausal status, vascular invasion, extracapsular extension and multifocallity/multicentricity. A P value of $<.05$ was considered statistically significant. The statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago IL).

RESULTS

Data for this retrospective analysis were obtained from 299 patients with operable HER2 breast cancer. Patient demographics and disease characteristics are described in Table 1. The mean age was 49.4 years. Overall, 155 patients were HR positive (51.8%), 122 (44.4%) had poorly differentiated tumors and 155 (51.8%) had vascular invasion. Involvement of lymph nodes was observed in 158 (52.8%) cases. Most patients underwent radical mastectomy (94.6%). Complementing this, the majority of the patients (76.9%) received adjuvant chemotherapy, but this included taxanes (not concurrently with anthracyclines) in only a small subgroup (3.0%) because taxanes were initially restricted to patients with more than three compromised lymph nodes. Almost all patients who received adjuvant endocrine therapy were HR+. Adjuvant treatment included radiation in 24.7% of patients mostly for axillary lymph node involvement and locally advanced stage. A reduced number of patients (7.4%) did not receive any adjuvant treatment, mostly due to a high risk of complications after individualized analysis.

Most of the well or moderately differentiated tumors were HR+ (61.4%) and most poorly differentiated tumors were HR– (50.4%). Additionally, extracapsular extension was more frequent (20.1%) in HR– patients. Aside from these differences, patient characteristics were comparable between the two groups in age, menopausal status, histological types, pTNM (stage I-II-III) status, type of initial therapy and use of adjuvant chemotherapy and radiation (Table 1). The most frequent recurrence locations were bone, lung, liver, and ipsilateral supraclavicular lymph nodes. In general, all recurrence locations except bone were more frequent in the HR– group (Table 2).

Table 1. Comparison of demographics, disease characteristics and treatment by hormone receptor status in early HER2 positive breast cancer patients.

Variable	All cases n=299	[HER2+, ER+ or PR+] n=155 (51.8%)	[HER2+ ER- and PR-] n=144 (48.2%)	*P*
Patient and disease characteristics				
Mean age ± SD (years)	49.4±11.0	49.5±11.0	49.3±11.0	.881
Premenopausal status n (%)	162 (54.2%)	87 (56.1%)	75 (52.1%)	.483
Mean tumor size ± SD (cm)	3.3±1.8	3.2±1.5	3.5±2.0	.106
Estrogen receptor positive	146 (48.8%)	146 (94.2%)	0 (0.0%)	<.0001
Progesterone receptor positive	114 (38.1%)	114 (73.5%)	0 (0.0%)	<.0001
T-status, n (%)				
T1	71 (24.1%)	41 (26.8%)	30 (21.3%)	
T2	185 (62.9%)	95 (62.1%)	90 (63.8%)	
T3	27 (9.2%)	13 (8.5%)	14 (9.9%)	.530
T4	11 (3.7%)	4 (2.6%)	7 (5.0%)	
Tx	5	2	3	
Lymph node compromise	158 (52.8%)	87 (56.1%)	71 (49.3%)	.238
AJCC stage, n (%)				
Stage I	47 (15.7%)	30 (19.4%)	17 (11.8%)	
Stage II	160 (53.5%)	83 (53.5%)	77 (53.5%)	.128
Stage III	92 (30.8%)	42 (27.1%)	50 (34.7%)	
Histologic grade (Elston/Ellis), n (%)				
Well differentiated	13 (4.7%)	10 (7.1%)	3 (2.2%)	
Moderately differentiated	140 (50.9%)	76 (54.3%)	64 (47.4%)	.043
Poorly differentiated	122 (44.4%)	54 (38.6%)	68 (50.4%)	
Unknown	24	15	9	
Vascular invasion	155 (51.8%)	82 (52.3%)	74 (51.4%)	.881
Extracapsular extension	44 (14.7%)	15 (9.7%)	29 (20.1%)	.011
Multifocality/multicentricity	31 (10.4%)	20 (12.9%)	11 (7.6%)	.136
Breast surgery, n (%)				
Mastectomy	283 (94.6%)	146 (94.2%)	137 (95.1%)	.717
Conservation	16 (5.4%)	9 (5.8%)	7 (4.9%)	
Adjuvant treatment, n (%)				
Chemotherapy	230 (76.9%)	113 (72.9%)	117 (81.3%)	.087
Taxane-containing	7 (3.0%)	5 (4.4%)	2 (1.7%)	.274
Radiation	74 (24.7%)	30 (19.4%)	44 (30.6%)	.025
Hormonal therapy	157 (52.5%)	135 (87.1%)	22 (15.3%)	<.0001
Tamoxifen	107 (68.2%)	88 (65.2%)	19 (86.4%)	
Aromatase inhibitor	45 (28.6%)	42 (31.1%)	3 (13.6%)	NA
Unknown[a]	5 (3.2%)	5 (3.7%)	0 (0.0%)	
No adjuvant treatment	22 (7.4%)	4 (2.6%)	18 (12.5%)	.001

[a]Study BiG1-98, ER: estrogen receptor, PR: progesterone receptor, NA: not applicable

Table 2. Observed first recurrences by hormone receptor status in early HER2 positive breast cancer patients.

Recurrence location	All cases		[Her2+, ER+ or PR+]		[Her2+, ER- and PR-]		
	Number of patients (n=90)	%	Number of patients (n=41)	%	Number of patients (n=49)	%	P[a]
Distant							
Bone	25	27.8%	14	34.1%	11	22.4%	0.217
Lung nodules	22	24.4%	8	19.5%	14	28.6%	0.319
Liver	17	18.9%	7	17.1%	10	20.4%	0.687
Central nervous system	8	8.9%	3	7.3%	5	10.2%	0.723
Subcutaneous and skin	11	12.2%	3	7.3%	8	16.3%	0.194
Contralateral breast	4	4.4%	2	4.9%	2	4.1%	0.999
Other places	18	20.0%	7	17.1%	11	22.4%	0.525
Locoregional							
Ipsilateral supraclavicular lymph nodes	16	17.8%	6	14.6%	10	20.4%	0.476
Mastectomy scar	10	11.1%	4	9.8%	6	12.2%	0.750
Ipsilateral axillary lymph nodes	2	2.2%	1	2.4%	1	2.0%	NA

[a]Chi-square test or exact test of Fisher, ER: estrogen receptor, PR: progesterone receptor, NA: not applicable

The median follow-up time for the total 299 patients was 93 months (range 12-115 months). During this period of observation, 90 (31.1%) patients developed disease recurrence at a local, regional or distal level and 55 (18.4%) deaths were registered.

In the complete data set, the mean DFS and OS were 4.24 and 4.60 years, respectively. Median for both parameters had not been reached at the time of analysis.

Steroid receptor status and survival

Analysis according to HR status revealed that the recurrence curve for the HER2+/ HR– group was always higher than for the HER2+/ HR+ group, the peak of recurrences for both groups being found during the second and third years after surgery; recurrences were rare after the fourth year (Figure 1). The distribution of the curves showed that recurrences in the HER2+/ HR– group were more frequent during the second year; this was followed by a steep fall, while the recurrences in the HER2+/ HR+ group were more constant during the four years.

In log-rank testing, HER2+/ HR– patients were significantly more likely to relapse than HER2+/ HR+ patients, giving 5-year breast cancer free survival rates of 65.0% and 74.6% (P=.045, Figure 2) and mean DFS of 3.97 and 4.38 years, respectively. Medians were not reached, but DFS rates were 71.4% and 65.0% at 3 and 5 years, respectively for HER2+/ HR– patients. Also DFS rates for HER2+/ HR+ patients were 83.1% and 74.6% at 3 and 5 years, respectively.

In the multivariate Cox regression analysis, the only covariable with a significant effect on the time to recurrence (besides the absence of HR, P=.022), was pathological compromise of axillary lymph nodes (P<.001). As such, the absence of HRs increased the recurrence risk by more than 1.7-fold over the presence of HRs (hazard ratio= 1.707, 95% CI; 1.079-2.699). Furthermore, N3 pathologic compromise increased the risk of recurrence by two-fold (hazard ratio=5.423, 95% CI; 2.823-10.418). Statistically significant differences were not reported in 5-year OS between the populations, being 75.5% and 82.4% for HER2+/ HR– and HER2+/ HR+ tumors (P=.140), respectively. Mean OS was 4.5 and 4.7 years for the absence and presence of HR, respectively (Figure 3).

DISCUSSION

Breast cancer is a heterogeneous disease. Despite the fact that data for hormone receptor and HER2 status are not as exact as genetic analyses, it is clear that receptor status information is much more readily available and can give us an extremely useful tool for obtaining information about the behavior of the disease in patients

in a clinic setting.[13,14] We evaluated a homogeneous set of patients with early breast cancer who had overexpression of *HER2*, and compared survival in the presence or absence of steroid receptors. With expression of at least one of the steroid receptors (estrogen or progesterone), a treatment decision was made (although controversial), based on the fact that the progesterone receptor gene is regulated by the estrogen pathway and the observation of a response to endocrine therapy is achieved in the expression of either receptor.

Our results show that for the overall HER2+ patient population, the HR– group has a higher rate of aggressive features such as poor differentiation and extracapsular extension than in the HR+ population. Furthermore, the absence of HR is associated with a higher risk of relapse at 5 years and a tendency towards earlier recurrences. Bone metastasis as the first location of recurrence was more common in the HR+ population. These results correlate with the findings of other studies, including the Carolina Breast Cancer Study which suggests a shorter DFS for HER+/ HR– versus HER+/ HR+ status for 5-year survival, with rates of 52% and 87%, respectively.[15] In addition, the HERA trial, which evaluated 1698 HER2+ early breast cancer patients in the non-trastuzumab (observational) arms, found a DFS at 3 years of 70% and 78% for the absence and presence of hormone receptor, respectively.[16] These and other studies also show differences in the pattern of relapses between the populations, with a very high risk of early recurrence for the absence of hormone receptor, but a consistently high risk over time for the presence of hormone receptor. Theses data are also in agreement with the association between the presence of bone metastases and HR positivity.[15-17] Response and recurrence patterns represents the interaction of several variables instead of the single poor prognosis–factors represented by the combination of HER2 overexpression and lack of hormonal receptors; for example, only HR patients benefit from adjuvant hormonal therapy, but the benefits for adjuvant chemotherapy are not great as compared with those for patients with ER-negative disease;[18] but in the subset of node positive HER2+ patients, ER-negative and ER-positive have a similar benefit from standard chemotherapy.[19]

Preclinical and clinical experience has demonstrated an additive effect when combining hormonal therapy and therapy targeted to HER2.[20-22] The HERA trial results show that trastuzumab has an additive effect to adjuvant hormonal therapy, producing a benefit that is independent of hormone status (increase in 3-year DFS of 6.1% and 6.6% for hormone receptor status negative and positive, respectively). However, the

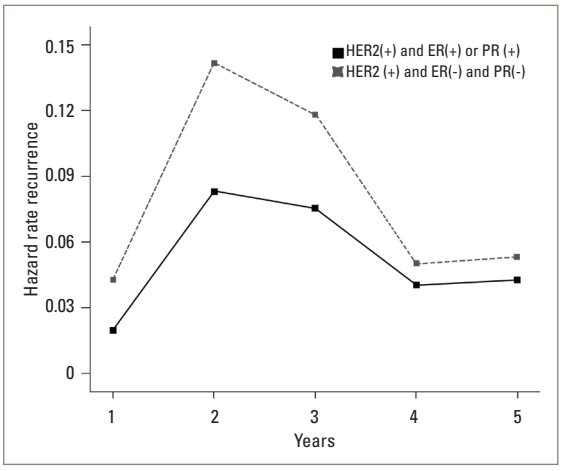

Figure 1. Recurrence in HER2 +/ HR- versus HER2 +/ HR+ populations.

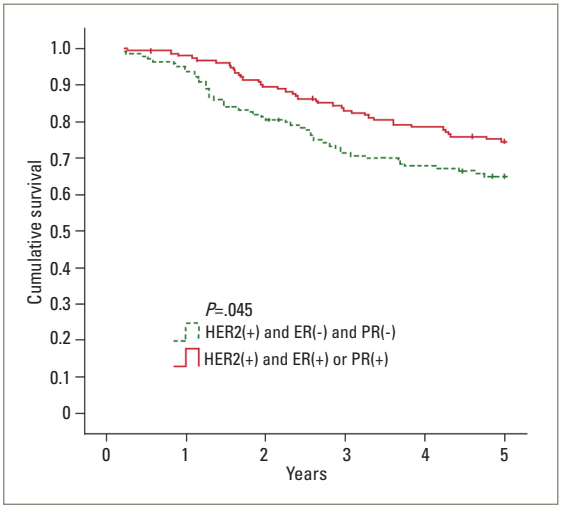

Figure 2. Disease-free survial in HER2 +/ HR- versus HER2 +/ HR+ populations.

pattern of treatment benefits over the recurrence risk may differ with follow-up, with a predominant activity preventing early recurrences in HR– and producing a sustained reduction in HR+ tumors.[16] Another point is the evidence that in patients overexpressing *HER2*, trastuzumab achieved a modest benefit in HR positive patients compared with HR negative patients, although this difference was not statistically significant.[16, 23]

In summary, we observed significant differences in histologic grade and extracapsular invasion in HR– and HR+ groups. This difference in pathologic characteristics could lead to a bias in our analysis of the impact of HR, but in a previous work in 1198 patients in our population we observed this difference, which could be explained by the tumor biology instead of

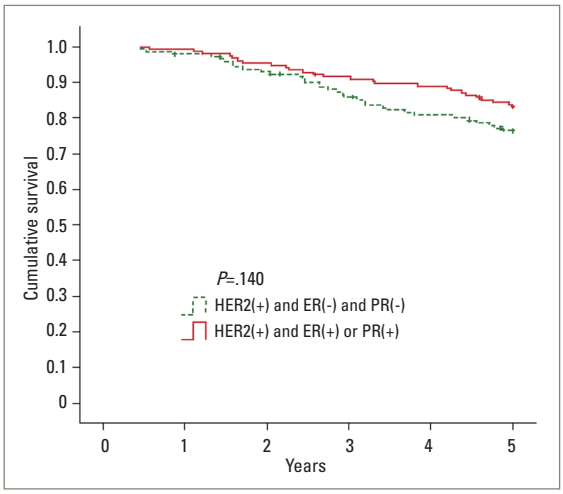

Figure 3. Overall survival in HER2 +/ HR- versus HER2 +/ HR+ populations.

sampling bias.[24] Our results suggest that in the early breast cancer patients with overexpression of *HER2*, the absence of hormone receptors is significantly associated with a more aggressive behavior and a poor prognosis. Despite of clinical evidence showing the benefit of adding trastuzumab to adjuvant treatment, the prognosis is slightly worse with positive hormonal receptor tumors.

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Author Contributions

Gomez: conception, design, acquisition of data, interpretation of data, writing of manuscript, Castaneda: conception, design, acquisition of data, Vigil: acquisition of data, Vidaurre: acquisition of data, Velarde: acquisition of data, Cruz: statistical analysis, Pinto: drafting of the manuscript, interpretation of data, Suazo: acquisition of data, Garces: acquisition of data, Neciosup: acquisition of data, Vallejos: design, final approval of manuscript.

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