Circulating HER2 Extracellular Domain and Resistance to Chemotherapy in Advanced Breast Cancer\(^1\)

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**ABSTRACT**

To test the hypothesis of an association between HER2 and chemotherapy resistance, we performed a prospective assessment of the predictive value of the circulating HER2 extracellular domain (ECD) in patients with advanced breast carcinoma in the setting of a multicenter Phase II trial using paclitaxel and doxorubicin. Serum samples were collected from 58 patients with metastatic breast carcinoma before first-line chemotherapy for advanced disease, and the levels of circulating HER2 ECD were measured using an enzyme immunoassay. Immunohistochemistry with anti-HER2 monoclonal antibody CB11 was used to assess the overexpression of HER2 in the primary tumors. When 450 fmol/ml was used as a cutoff, 24 cases (41%) had elevated HER2 ECD levels. Elevated levels of circulating HER2 ECD were associated with the expression of HER2 in the primary tumor tissue and with the metastatic tumor burden (evaluated with the marker CA 15-3; \(P = 0.032\) and \(P = 0.002\), respectively) but not with variables such as menopausal status, stage at diagnosis, previous adjuvant therapy, or the number of metastatic sites. The levels of circulating HER2 ECD correlated inversely with the response to treatment. The probability of obtaining a complete response to chemotherapy was significantly lower \((P = 0.021)\) in patients with elevated HER2 ECD levels \(0\% \); 95% confidence interval, 0–13%) compared with patients with nonelevated HER2 (26%; 95% confidence interval, 12–45%). In addition, the duration of clinical response was significantly shorter in patients with elevated HER2 ECD, compared with the cases with nonelevated HER2 \(7.5 \text{ versus } 11\) months; \(P = 0.035\).

In conclusion, elevated levels of circulating HER2 ECD in patients with metastatic breast cancer correlate with reduced efficacy of a paclitaxel-doxorubicin chemotherapy combination. We suggest that the poor response rate associated with HER2 expression in advanced breast cancer may not be reversed by aggressive chemotherapy alone.

**INTRODUCTION**

Some genetic disorders in breast cancer have been associated with a poor prognosis. One of these disorders is the amplification of the HER2 oncogene \((1)\). The HER2 oncogene (also named erbB-2 and HER2/neu) codifies for the HER2 oncoprotein \((\text{also called p185}^{\text{erbB-2}})\), which has a structure of growth factor receptor \((2)\). The HER2 ECD \(^3\) can be found in the circulation \((3, 4)\). Overexpression of the HER2 oncoprotein in primary breast carcinomas \((5)\) and in serum \((6)\) has been related to a higher relapse rate.

The adverse prognostic effect of HER2 overexpression may be related to the resistance to chemotherapy \((7)\). Two neoadjuvant (preoperative) chemotherapy studies (using mitoxantrone plus methotrexate and CAF/cyclophosphamide-epirubicin-5-fluorouracil, respectively) have found a negative association of HER2 expression with response \((8, 9)\). Furthermore, in metastatic breast carcinoma, two retrospective studies have found an inverse relationship between HER2 expression in primary tumor tissue \((10)\) or serum \((11)\) and the response to single agent mitoxantrone or cyclophosphamide-Novanthron-fluorouracil, respectively. In the adjuvant setting, the predictive value of HER2 is controversial \((7)\). Four studies using CMF or CMF-like adjuvant chemotherapy (International Breast Cancer Study Group study V, Intergroup 0011, Guy’s/Manchester, and Stockholm Breast Cancer Group) have shown that tumors that overexpress HER2 have shorter disease-free survival times than those with normal amounts of HER2 gene product \((12–15)\). No such lack of benefit was noted, however, when conventional doses of adjuvant CAF (CALGB 8541, and its ancillary study 8869; Ref. 16), PAF (National Surgical Adjuvant Breast and Bowel Project study B-11; Ref. 17), or a single cycle of perioperative CAF (European Organization for Research and Treatment of Cancer study 10854; Ref. 18) were used.

The study that we performed is the first prospective assessment of the predictive value of HER2 ECD expression in metastatic breast carcinoma. We report the clinical outcome of

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\(^3\) The abbreviations used are: ECD, extracellular domain; CAF, cyclophosphamide-Adriamycin-5-fluorouracil; CMF, cyclophosphamide-methotrexate-5-fluorouracil; CALGB, Cancer and Leukemia Group B; PAF, l-phenylalanine mustard-5-fluorouracil-doxorubicin; CI, confidence interval.
58 patients with advanced breast cancer treated with a first-line chemotherapy combination of paclitaxel and doxorubicin and analyzed for the expression of HER2 in the serum and primary tumor tissue. We show that the efficacy of treatment (measured as the response rate and the duration of response) is significantly impaired in patients who express elevated levels of circulating HER2 ECD.

MATERIALS AND METHODS

Patients. Patients included in this study had measurable metastatic breast carcinoma and had not received previous chemotherapy for advanced disease. Before treatment, a 10-ml blood sample was drawn and centrifuged at 1000 × g for 5 min. Serum was aliquoted in two parts and stored in polypropylene cryotubes at −20°C.

The clinical variables that were recorded were as follows: menopausal status, estrogen receptor status, stage at first diagnosis (relapsing versus initially metastatic), previous adjuvant chemotherapy, number of metastatic sites, dominant site of metastases, and the tumor marker CA 15-3, which previously had been associated with metastatic breast cancer burden (19). When possible, paraffin blocks from the primary breast carcinomas were collected, and immunohistochemical analysis was performed.

Seventy-seven patients participated in the Phase II clinical trial. Fifty-eight had serum samples evaluable for circulating HER2. In 40 cases, HER2 expression was determined in primary tumor tissue.

Chemotherapy. The chemotherapy regimen used was a combination of doxorubicin (50 mg/m²), followed by a 3-h infusion of paclitaxel (175 mg/m²), administered every 21 days for six to nine cycles (Spanish Ministry of Health protocol no. 94/20). Treatment efficacy was evaluated by each of the investigators, and responses were confirmed by an independent panel of experts (two radiologists and one medical oncologist). No local treatments were allowed in the target lesions. Efficacy parameters used for this analysis were objective response rate, as defined by WHO criteria, and duration of response, defined as the time elapsed from the achievement of an objective response until disease progression. The results of the Phase II trial will be reported elsewhere.4 Median follow-up at the time of the analysis was 23 months. Twenty-seven patients had received previous adjuvant tamoxifen, and 27 patients had received tamoxifen for metastatic disease.

HER2 Measurements. The levels of circulating HER2 were measured using a sandwich enzyme immunoassay, according to the manufacturer’s instructions (Human neu quantitative ELISA; Calbiochem; Ref. 20). The HER2 ECD values are expressed in fmol/ml.

Immunostaining for HER2 in primary carcinomas was performed using the anti-c-HER2 antibody CB11 (Biogenex) at a dilution of 1:80, and a streptavidin-biotin detection system (kit LSAB2; DAKO). Development was performed with diaminobenzidine, using Harris’ hematoxylin counterstain. Membrane HER2 staining was quantified in percentages (0–100%). Cases were considered positive when 10% or more of tumor cells had intense membrane staining.

Statistical Methods. The association of HER2 with clinical parameters was evaluated with the ß2 test, using the Mantel-Haenszel test to evaluate linear associations. Multivariate analysis of categorical variables was performed using logistic regression. Correlations were performed using the Spearman test. The Mann-Whitney ß test was used to test differences between mean values of subgroups. To evaluate the duration of response, the Kaplan-Meier estimation was used, and comparisons were made with the log-rank test. For multivariate analysis of time-dependent variables, the Cox proportional hazards regression model was used.

RESULTS

HER2 Levels in Serum and Tumor Tissue. Circulating HER2 ECD levels ranged from 155 to 38,871 fmol/ml (median, 427 fmol/ml). Mean levels were 2085 fmol/ml, with a SE of 810 fmol/ml. When we used 450 fmol/ml as the cutoff level, 24 cases had elevated levels of HER2 (41%) and 34 cases had nonelevated values (59%).

To test the specificity of circulating HER2 ECD in advanced breast cancer, we determined the expression of HER2 in 40 of the primary breast carcinomas. As can be seen in Table 1,
HER2 ECD and Chemotherapy in Metastatic Breast Cancer

A logistic regression analysis showed that only tissue variables and tissue HER2 on the elevation of circulating HER2 ECD and the extent of metastatic breast cancer. Confirms the association between the levels of circulating HER2 and in tumor tissue were significantly associated (P = 0.032).

Correlation of Circulating HER2 ECD and Clinical Parameters. We performed correlations between circulating HER2 ECD and several clinical parameters. The results are shown in Table 1. Menopausal status, estrogen receptor status, stage at diagnosis (relapsing versus initially metastatic), previous adjuvant chemotherapy, dominant site of metastases, and the number of metastatic sites did not correlate with HER2. However, elevated circulating HER2 ECD levels were associated significantly with positivity for the tumor marker CA 15-3 (P = 0.002), indicating that the expression of HER2 in the serum is associated with metastatic tumor burden in patients with advanced breast carcinoma.

Table 2  Correlation of the response to chemotherapy with circulating HER2 ECD levels, tissue HER2 expression, and the levels of CA 15-3

<table>
<thead>
<tr>
<th>Objective response</th>
<th>Circulating HER2</th>
<th>Tissue HER2</th>
<th>CA 15-3 levels</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Nonelevated</td>
<td>Elevated</td>
<td>Negative</td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (26%)</td>
<td>0 (0%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (52%)</td>
<td>15 (62%)</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>No response</td>
<td>7 (23%)</td>
<td>9 (37%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>

P = 0.021 0.219 0.043

Fig. 1  Response duration stratified by HER2 ECD status. The Kaplan-Meier plot shows that patients with elevated HER2 ECD (——–) had shorter duration of response than patients with nonelevated HER2 (—). The difference was significant using the log-rank test (P = 0.035).

We also evaluated the efficacy of treatment using the duration of response. Overall median duration of response was 10 months (95% CI, 7–12 months). When we compared the duration of response in the patients with elevated or nonelevated levels of circulating HER2 ECD, we found that there were statistically significant differences (7.5 versus 11 months; P = 0.035). Fig. 1 illustrates that elevated circulating HER2 ECD levels are associated with a shorter response duration. We also performed a Cox analysis of the response duration using HER2 ECD as a continuous variable. This analysis showed that HER2 ECD had a borderline statistical significance (P = 0.06).

Because previous treatment with adjuvant anthracyclines might have an impact on the interaction of HER2 with the chemotherapy that we used in the metastatic setting (paclitaxel and doxorubicin), we performed an analysis of treatment efficacy, removing the 16 patients with past anthracycline exposure. Again the duration of response was shorter in the HER2 ECD-positive patients than in the HER2 ECD-negative patients (6.4 versus 14.9 months; P = 0.07).

Table 2 shows that 0% of the patients with elevated HER2 had a complete response (95% CI, 0−13%), whereas 26% of patients with nonelevated HER2 had a complete clinical response (95% CI, 12−45%). In addition, almost twice the proportion of cases with elevated HER2 did not respond to therapy when compared with the cases with nonelevated HER2 (37 versus 23%; 95% CI, 19−59% and 10−41%, respectively). Therefore, there was a statistically significant inverse relation-

73% of cases expressing HER2 in the primary tumor had elevated circulating HER2 ECD at relapse, and 66% of the cases negative in the primary tumor were also negative when they developed metastasis. Therefore, HER2 expression in the serum and in tumor tissue were significantly associated (P = 0.032).

Correlation of Circulating HER2 ECD and Treatment Efficacy. Treatment efficacy was evaluable in 55 of the cases with circulating HER2 measurement. Three patients were not evaluable for response: one patient had a lung embolism after the first cycle; one patient had a hypersensitivity adverse event; one patient had only nonmeasurable bone lesions.

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ship between the levels of circulating HER2 and the clinical response (P = 0.021).

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showed a significant association in the multivariate analysis. The circulating HER2 level was the only variable that responded (response versus no response). Therefore, circulating HER2 ECD is a significant predictor of treatment efficacy in comparison with other variables, we performed multivariate analyses (Table 3). Tissue HER2 was not introduced in the models because it compromised the number of cases. We explored the correlation between the efficacy of chemotherapy and the levels of CA 15-3. Table 2 shows that there was a trend for tissue HER2 expression to correlate inversely with the response to treatment. However, in this case the association was not significant.

On the other hand, CA 15-3 levels in patients with advanced breast carcinoma showed a significant inverse correlation with the response to chemotherapy. As can be seen in Table 2, positive CA 15-3 levels were associated with a lower probability of obtaining a complete response. CA 15-3 levels, however, did not correlate with a higher probability of not responding.

**Multivariate Analysis of Treatment Efficacy.** To assess the relative importance of circulating HER2 on treatment efficacy in comparison with other variables, we performed multivariate analyses (Table 3). Tissue HER2 was not introduced in the models because it compromised the number of cases. We first performed a logistic regression analysis, using objective response (response versus no response) as the dependent variable. The circulating HER2 level was the only variable that showed a significant association in the multivariate analysis ($P = 0.03$). Second, we performed a Cox regression analysis of the duration of response. This showed that of the variables entered in the model, only circulating HER2 ECD retained statistical significance in the multivariate analysis ($P = 0.04$). Therefore, circulating HER2 ECD is a significant predictor of treatment efficacy that is independent of other clinical variables.

**DISCUSSION**

HER2 oncogene expression has been related to an unfavorable prognosis in breast cancer (1, 5). Several retrospective studies have suggested that HER2 expression is associated with a reduced efficacy of adjuvant chemotherapy (7). Our study has confirmed this point in a different patient population by finding that the expression of HER2 ECD in the prospectively collected sera of patients with advanced breast cancer correlates inversely with the response to chemotherapy. In our study, we observed marked differences in the probability of response between the cases that had elevated circulating HER2 ECD and the cases with nonelevated HER2. In addition, the quality of the responses was affected by HER2 ECD expression because the duration of response was significantly shorter in patients with elevated circulating HER2 ECD than in patients with nonelevated HER2 ECD (7.5 versus 11 months).

In the present study, the distribution of HER2 levels in the serum of patients with advanced breast cancer is similar to the distribution we found in a previous study in which the same assay was used (21). We categorized the levels of circulating HER2 ECD using 450 fmol/ml as a cutoff. The proportion of cases with elevated HER2 in our study was identical to the positivity rate that has been reported by other authors in patients with metastatic breast cancer using the same or similar ELISAs (43, 45, and 34%, respectively; Refs. 22–24).

Our results showing a relationship of HER2 ECD expression and resistance to chemotherapy are consistent with several reports in the adjuvant and neoadjuvant settings. Retrospective analysis of adjuvant chemotherapy in node-negative patients, such as the International Breast Cancer Study Group study V (12) and the Intergroup study 0011 (13), and in node-positive patients, such as the Guy’s/Manchester (14), have showed that adjuvant CMF chemotherapy has reduced efficacy in the subset of HER2-positive patients. A study by Fehm et al. (6) in node-positive breast carcinoma found that HER2 ECD-positive patients had a worse outcome than HER2-negative patients when treated with either adjuvant CMF or cyclophosphamide-Novantrone-fluorouracil. Two recent prospective studies have evaluated the efficacy of preoperative chemotherapy in relation with HER2 status (8, 9). In the study by Makris et al. (8), the response rate was significantly lower in HER2-positive than in HER2-negative cases (57 versus 93%; $P = 0.007$), and in the report by Vargas-Roig et al. (9), 89% of HER2-positive patients developed distant metastases, whereas only 38% of the HER2-negative cases did ($P = 0.006$). The results of the present study are further supported by a subsequent study of HER2 ECD that we have carried out in 43 patients with metastatic breast cancer treated with a biweekly combination of paclitaxel and gemcitabine. In this study, which used the same HER2 ECD test and cutoff, the response rate to paclitaxel-gemcitabine was 85% in HER2 ECD-positive patients and 40% in the HER2-negative cases ($P = 0.003$), and the duration of response was 6 and 10.5 months, respectively ($P = 0.06$; Ref. 25).

Other studies, in contrast, have not found an association between HER2 expression and resistance to chemotherapy. The

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariate analysis of response rate and duration of response</th>
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<tr>
<td><strong>Response rate</strong></td>
<td><strong>Duration of response</strong></td>
</tr>
<tr>
<td></td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>Univariate $P$</td>
</tr>
<tr>
<td>Menopausal status (Pre vs. post)</td>
<td>0.39</td>
</tr>
<tr>
<td>Type of advanced disease (Relapse vs. initially metastatic)</td>
<td>0.79</td>
</tr>
<tr>
<td>Adjuvant chemotherapy (None vs. non-anthracycline vs. anthracycline)</td>
<td>0.91</td>
</tr>
<tr>
<td>Number of metastatic sites (1 vs. ≥2)</td>
<td>0.32</td>
</tr>
<tr>
<td>CA 15-3 levels (&lt;30 vs. ≥30 units/ml)</td>
<td>0.36</td>
</tr>
<tr>
<td>Circulating HER2 ECD (&lt;450 vs. ≥450 fmol/ml)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

$^a$ Response vs. no response.
$^b$ Relative risk (95% CI).
CALGB study 8869 (16) evaluated three doses of adjuvant CAF chemotherapy (standard, low, or very low) in 396 cases with node-positive breast cancer. They found that standard CAF was more active than the lower doses and that this was especially true in the HER2-positive cases. The National Surgical Adjuvant Breast and Bowel Project study B-11 showed that PAF adjuvant treatment in ER-negative, node-positive patients was superior to L-phenylalanine mustard-5-fluorouracil. An evaluation of HER2 expression in this study (17) observed that the benefit of PAF is restricted to HER2-positive patients. Because some of the drugs in the CMF and L-phenylalanine mustard-5-fluorouracil regimens are identical to those in CAF or PAF, it has been hypothesized that doxorubicin, the drug that is not common in the comparative regimens, may be more active in HER2-positive cases. A recent update of CALGB study 8541/8869, however, although validating the results in the 396 cases of the first report, has not to replicate the results in an additional cohort of 595 patients (26). Two published retrospective studies, one in primary breast cancer (27) and another in advanced breast cancer (28), have not found a correlation between treatment response to CAF and HER2 tumor expression. The retrospective design of all of these studies and the limitations of immunohistochemical analysis in archival samples (29, 30) may explain some of the discrepancies observed and make the point for prospectively designed trials when evaluating biological endpoints.

In our study, we used a combination of doxorubicin and paclitaxel, two drugs that have been suggested to be more active in HER2-positive breast cancer (16, 17, 31). The design of our single-arm study does not allow a conclusion about the interaction between HER2 expression and the individual efficacy of doxorubicin or paclitaxel. HER2-associated chemoresistance has been reported to be independent of the multidrug resistance gene mdr-1 (32), and recent animal experiments using cells transfected with HER2 have suggested that the lack of response to chemotherapy of HER2-positive tumors is related to the rapid proliferation of the tumor cells that survive the chemotherapy and not to an intrinsic resistance to chemotherapy (33). In agreement with these observations, a recent investigation in which the apoptotic index was measured in primary breast carcinomas before and 24 h after doxorubicin-containing chemotherapy showed that HER2-positive tumors have a markedly reduced apoptotic response to chemotherapy (34). Therefore, the expression of HER2 may not indicate a pleiotropic resistance to chemotherapy, but rather it represents a cellular growth advantage that allows the regrowth of tumor cells after treatment. This is consistent with the shorter duration of responses that we observed in the cases with elevated circulating HER2 ECD.

In our study, we observed a significant association of circulating HER2 ECD levels in the serum with the expression of HER2 in the primary tumor, although the assay reagents used for the detection of HER2 in the serum and in the tumor were not the same. Our results agree with the concordance indices for HER2 of 70–80% that have been reported with variations in the diagnostic HER2 antibodies (30). In our series, circulating HER2 ECD levels also correlated with an indicator of tumor burden, the marker CA 15-3, reflecting that HER2 ECD levels in the serum depend on the amount of metastatic tumor cells. This is in agreement with the results of Krainer et al. (35), who found a very similar correlation coefficient between serum HER2 ECD and CA 15-3 in patients with metastatic breast cancer. The detection of elevated HER2 ECD levels in the absence of HER2 overexpression in the primary tumor tissue reflects the different timeframes in the collection of samples. Whereas HER2 was determined at the time of primary surgery, HER2 ECD was determined much later in the disease course, when distant metastases were present. It has been suggested that HER2 amplification may be involved in the progression of breast cancer from a hormone-dependent to a hormone-independent phenotype. A study of multiple biopsies of patients with advanced breast cancer undergoing hormonal treatment showed that HER2 amplification appeared (9–31 months after the initiation of therapy) in 6 of 34 HER2-negative cases (36).

Our data suggest that circulating HER2 ECD levels may be a better indicator of resistance to chemotherapy than the expression of HER2 in the primary tumor. However, the small number of cases in which we could determine tissue HER2 and the different methods of tumor tissue processing that were used in each of the centers participating in the study do not allow a definitive conclusion. An advantage for the use of serum samples over archival tissue in patients with advanced breast carcinoma is that, in general, serum samples may be obtained more easily after relapse. Therefore, the measurement of circulating HER2 in the serum may be more reliable and reproducible than the measurement of HER2 in archival paraffin blocks. Our study cannot distinguish whether HER2 ECD predicts for resistance to paclitaxel or to doxorubicin because we used the drugs in combination. The Eastern Cooperative Oncology Group study 1193 measured circulating HER2 in patients with advanced breast cancer that received paclitaxel, doxorubicin, or the combination paclitaxel-doxorubicin. The results from this study will provide important information on this issue when they are published. Our clinical trial did not include an untreated control arm, an instance difficult to justify in the management of advanced breast carcinoma. Therefore, the value of circulating HER2 ECD as either a pure predictive factor (related only to chemotherapy) or a mixed predictive/prognostic factor (related to chemotherapy and also to intrinsic disease characteristics) cannot be fully established from our results (37).

With the evidence provided in our study, a recommendation for selecting conventional chemotherapy regimens in advanced breast cancer based on HER2 status is not justified. In contrast, we suggest that the poor response rate that is associated with HER2 expression might be reversed with anti-HER2-specific therapies, an approach that has been effective in the laboratory (38, 39) and in randomized clinical trials (40) with monoclonal antibodies.

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