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Original article

# Outcomes of Hispanic women with lymph-node positive, HER2 positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab in Mexico

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ABSTRACT

*Introduction:* Evidence regarding the outcomes of Hispanic women with breast cancer is lacking. We analyzed women with HER2+ disease treated with trastuzumab-based neoadjuvant chemotherapy in Mexico.
*Methods:* 244 patients were included. Outcomes were compared between patients who achieved pathologic complete response (pCR) (n = 119), or less than pCR (n = 125). Patients with noninvasive (ypT0/is, ypN0) residual disease were also analyzed.
*Results:* 119 (48.8%) patients achieved pCR. pCR was the only factor associated with improved 3 year survival (98.1% vs 92.3%: P = 0.02). Survival was better in patients with ypT0/is, ypN0 response than in those with residual invasive disease (p < 0.01). 3 year survival was 98.1% for patients with pCR and 92.6% for patients with ypTis, ypN0 response (p = 0.64).
*Conclusions:* Response rates to trastuzumab based neoadjuvant chemotherapy in Hispanics mimic that of other ethnic groups. This underlines the fact that access to treatment, rather than ethnicity, is the main prognostic factor in this population.



## Introduction

The Hispanic population is the fastest growing major demographic group in the United States, and by 2050 it will represent about 30% of the U.S. population [1]. The majority of Hispanics living in the U.S. are of Mexican origin (63%) [2]. Currently, breast cancer represents the most common malignancy among Hispanic women in the U.S., as well as the main cause of cancer-related mortality in this population [2]. Recent data from Mexico mirror these figures, and breast cancer is, since 2006, the leading cause of cancer mortality in Mexican women, accounting for 14% of cancer-related deaths [3]. Hispanic women have a lower incidence of

*Abbreviations:* HR, hormone receptor; RFS, recurrence-free survival; OS, overall survival; pCR, pathologic complete response; INCan, National Cancer Institute of Mexico; ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistry; Mo, months.

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breast cancer but a higher breast cancer-related mortality rate compared with white women [4]. There is some evidence that points towards the fact that this is particularly true for women with hormone receptor (HR) negative breast cancer subtypes, both triple negative and HR−/HER2+ [5].

The overexpression of human epidermal growth factor receptor type 2 (HER2) occurs in approximately 20–25% of breast carcinomas, and is associated with a high risk of poor outcomes and recurrence [6]. These figures have been confirmed in Hispanic patients treated in the U.S. [5,7]. In both the adjuvant and metastatic setting, randomized studies have highlighted the role of anti-HER2 agent trastuzumab in improving disease-free survival (DFS) and overall survival (OS) compared to chemotherapy alone [8–10]. In the neoadjuvant setting, the achievement of a pathologic complete response (pCR) with chemotherapy plus trastuzumab has been shown to correlate with survival outcomes [11–15]. This, however, may not be true for all types of breast cancer and for all ethnicities, and the magnitude of the benefit may be different among HER2 positive subgroups [7,16].

In the clinical setting, there are several potential advantages to neoadjuvant chemotherapy besides improved tumor resectability. Given that a pCR is a surrogate marker for improved clinical outcome, neoadjuvant therapy provides a window of opportunity to identify biomarkers and predictors of response and allows *in vivo* assessment of tumor response to drug therapies.

Our primary objective was to analyze the value of achieving a pCR after neoadjuvant trastuzumab-based chemotherapy in terms of DFS and OS in Mexican women with HER2+ breast cancer. We also evaluated the prognostic value of several clinical and histopathological factors in the achievement of a pCR.

## Methods

We conducted an observational retrospective cohort medical record review study. Between January 2007 and May 2012, consecutive cases of patients with the diagnosis of localized HER2+ breast cancer who received neoadjuvant trastuzumab-based chemotherapy and underwent surgery after its completion at the *Instituto Nacional de Cancerología* (INCan) of Mexico were retrieved from our archives. Ethical approval for all observational research was obtained from INCan Ethics Committee. As the study had no direct patient involvement and minimum risk, patient consent was not required. Patient characteristics including age, stage at diagnosis, type of neoadjuvant chemotherapy, site of relapse, and DFS and OS were recorded. The number of cases treated at INCan during the study period determined the sample size.

All pathology assessments were performed at the Pathology Department of INCan by dedicated breast pathologists. Each sample was analyzed using the same procedures and the same standardized assays. Estrogen receptor (ER) and progesterone receptor (PR) were determined by immunohistochemistry (IHC). Cases were classified as HR positive in case of ER and/or PR positivity and HR negative in case of both ER and PR negativity according to the Allred score. HER2 was determined initially by IHC and considered negative in cases of 0 (no membrane staining) or 1+ (weak and incomplete membrane staining) scoring. Tumors were considered HER2+ in cases of 3+ IHC staining or amplified FISH (ratio of HER2 to CEP17 of >2.2 or average HER2 gene copy number >six signals/nucleus) and HER2- in cases with 0, 1+ and 2+ IHC plus negative FISH amplification.

Clinical and radiographic staging procedures were used for all patients. T stage was defined using ultrasound measurements. Clinical N stage was defined by either the presence of palpable axillary lymph nodes or of abnormal lymph nodes upon ultrasound examination. Metastatic disease was excluded using tomographic assessment of the thorax and abdomen when indicated. All patients received neoadjuvant chemotherapy with taxanes and anthracyclines plus trastuzumab. 226 patients (92.6%) received trastuzumab concurrently with taxanes only, and 18 (7.4%) with both taxanes and anthracyclines. After completion of neoadjuvant chemotherapy, all patients underwent surgery (total mastectomy with axillary lymph node evaluation or breast conserving surgery). All patients treated with breast conserving procedures received adjuvant radiotherapy, and patients treated with mastectomy received adjuvant radiotherapy according to current guidelines. Endocrine therapy was prescribed as indicated in HR-positive patients.

pCR was defined as a complete absence of any residual invasive and in situ cancer in the breast and absence of any metastatic cells in the regional lymph nodes (ypT0, ypN0). Patients with no invasive residual in breast or nodes but with noninvasive breast residuals allowed (ypT0/is, ypN0) were also analyzed. The presence of invasive residuals in either the breast or axilla was considered as residual invasive disease.

After completion of treatment patients were reviewed by the Breast Cancer Unit at INCan using current guidelines for follow-up of breast cancer patients. Both DFS and OS were calculated from the date of diagnosis to the date of relapse, last relapse-free visit or death.

All data are presented as medians, means or proportions. Statistical analysis was carried out using SPSS (SPSS, Inc. Chicago, IL, v21.0) and Stata (StataCorp LP, College Station, TX, v12). The influence of baseline characteristics on the likelihood of achieving a pCR was tested in univariate analysis by using the test. The independent significance of these variables was assessed using a generalized linear model for multivariate analysis. The odds ratio of a pCR was calculated by using this model. Kaplan–Meier analysis was used to calculate survival outcomes. In order to estimate relapse and survival risk between different subgroups, we used a Cox proportional hazards regression model. Covariates in the model included HR status, age, clinical T-stage, clinical N-stage, type of pathological response, presence of inflammatory breast cancer and sequence of neoadjuvant chemotherapy. All *P* values presented are 2 sided, and *P* values <0.05 were considered statistically significant.

## Results

### *Patient characteristics*

A total of 244 Mexican women with HER2+ breast cancer who received neoadjuvant treatment with trastuzumab-based chemotherapy and underwent surgery after its completion were identified and considered eligible for analysis. Median age was 49 years (range, 26–72 years). The median tumor size was 5.5 cm (range, 1.5–20 cm) and 96% of patients had clinically positive axillary lymph nodes detected by palpation at diagnosis. 27% of tumors were categorized as T4 and 49% of patients had either N2 or N3 clinical regional lymph nodes. 48.8% of the tumors were considered HR positive and 51.2% negative. Of the 244 tumors, 27 (11.1%) fulfilled the criteria for inflammatory breast carcinoma. The median follow-up was 47 mo (12–78).

The characteristics of the patients are summarized in Table 1.

### *pCR in the breast and axillary lymph nodes*

Between January 2007 and May 2012, 244 patients with HER2+ breast cancer had surgery after receiving trastuzumab-based neoadjuvant chemotherapy. A pCR was achieved in 119 (48.8%) patients. ypT0/is, ypN0 response was found in 181 (74.2%) patients. Residual invasive disease was found in 63 (25.8%) patients.