Breast cancer survival by immunohistochemistry-determined subtype: A retrospective study

Aura Erazo Valle-Solís¹, Arturo Pabel Miranda-Aguirre¹, Josué Mora-Pérez², Juan Antonio Pineda-Juárez³, Luis Ernesto Gallardo-Valencia⁴, Liberio Santana⁴, Guadalupe Cervantes-Sánchez⁵ and Eduardo Cárdenas-Cárdenas^{5*}

¹Neoplastic and Proliferative Disorders Division; ²Teaching and Research Sub-directorate; ³Biomedical Research Division; ⁴General Management; ⁵Department of Medical Oncology. Centro Médico Nacional 20 de Noviembre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, City of Mexico, Mexico

Abstract

Background: Breast cancer subtype classification according to hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2) using immunohistochemistry is the standard practice for therapeutic decision making. **Objective:** To design future studies information on characteristics and survival of each subtype is essential. **Method:** We conducted a retrospective study to analyze clinical and pathologic features as well as survival data according to breast cancer immunohistochemistry subtype. **Results:** There were 211 women with a RH(+)/HER2(-) breast cancer subtype, 53 HR(+)/HER2(+), 16 HER2(+) and 23 HR(-)/HER2(-), with a median overall survival in months of 39 (20.5-62.7), 42 (25.5-65), 42 (13.7-67.7) and 26 (11-78), respectively, for a 3.7 hazard ratio of death (95% Confidence Interval [CI]: 1.3-10.3) for the triple negative group as compared to the HR(+)/HER2(-) group ($p = 0.01$). **Conclusions:** HR positive subtypes by immunohistochemistry where most frequent and showed a greater overall survival compared to the triple negative subtype.

KEY WORDS: Breast cancer. Immunohistochemistry. Molecular subtype. Survival.

Introduction

Breast cancer is the second most common neoplasm in the world and the most frequent in women. According to the World Health Organization (WHO), for the year of 2018, a total of 2.1 million new cases were estimated, accounting for 11.6% of all neoplasms. In addition, the WHO also estimated for that year a total of 626,679 deaths due to this condition¹. Furthermore, breast cancer is also considered the fifth cause of death from cancer in the world and a public health problem².

In Mexico, breast cancer has been considered a public health problem since 2006, when it surpassed cervical cancer as the leading cause of cancer-related death in the country³. Current incidence is not well known; however, official figures from the National Institute of Statistics and Geography (INEGI – *Instituto Nacional de Estadística y Geografía*) reported that

during 2012 there were 26.6 cases per 100 thousand women older than 20 years and, during 2013, 26.2 cases in the same age group, which accounted for 30.8% of tumors detected in women⁴. More concerning is the fact that the breast cancer mortality rate increased from 8.4 deaths per 100,000 population in 2005 to 10.1 deaths per 100,000 in 2015⁵.

Currently, thanks to the advances in the field of molecular biology, breast cancer has been classified into four molecular subtypes, which Perou et al.⁶ describe, based on their gene expression, as luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) overexpression and basal. Clinical evolution of each breast cancer molecular subtype is different and sets the standard for treatment along with other clinico-pathological characteristics. Thus, luminal tumors, which are characterized by the expression of hormone

Correspondence:

*Eduardo Cárdenas-Cárdenas
E-mail: carcardo84@hotmail.com

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receptors (HR) and a less aggressive behavior, benefit from hormone therapy with or without chemotherapy. Those that overexpress HER2 have a more aggressive behavior and benefit from targeted therapies such as trastuzumab and pertuzumab in combination with chemotherapy. Finally, basal-like neoplasms are mainly treated with chemotherapy and have the worst prognosis due to their biological behavior and fewer therapeutic options in comparison with the previously mentioned subtypes⁷⁻⁹.

Access to these genomic signatures for the classification of breast cancer is limited and, therefore, therapeutic decision-making in clinical practice is based on an approach to these subtypes by immunohistochemistry (IHC) analysis of estrogen, progesterone and HER2 receptor status, which yields the HR(+), HER2(-), HR(+) HER2(+), HR (-)/HER2 (+) and HR (-)/HER2 (-) subtypes, which are equivalent to the luminal, luminal B HER2(+), HER2-overexpressing and basal-like subtypes of the molecular classification¹⁰⁻¹².

Knowing the behavior of these breast cancer subtypes in our population is essential in order to be able to design new lines of research in this group of patients and, for this reason, we undertook the following study, whose purpose was to perform a retrospective review of breast cancer subtypes clinicopathological characteristics by means of IHC and associated survival.

Method

A retrospective cohort study was conducted at the National Medical Center *20 de Noviembre*, of the Institute of Social Security and Services of State Workers (ISSSTE – *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado*), of Mexico City, Mexico. Patient data were obtained from information registries and patient records of the period encompassed from January 2004 to December 2015. Approval of the study and data registration were authorized by the hospital's research, ethics and biosafety committees.

Female patients older than 18 years with a histopathological diagnosis of breast cancer were included. Patients were identified according to the presence or not of estrogen, progesterone and HER2 receptors; subsequently they were sub-classified into the following subtypes by IHC: 1) HR(+)/HER2(-); 2) HR(+)/HER2(+); 3) HER2(+), and 4) HR(-)/HER2(-). In addition, demographic variables (age), clinical variables (disease stage, positive lymph nodes, tumor size) and type of treatment (surgery, chemotherapy, radiotherapy, hormone therapy) were analyzed.

Overall survival was defined as the time elapsed from breast cancer initial diagnosis to the death of the patient and disease or progression-free survival as the time elapsed from the start of treatment to the recurrence or progression of the disease.

Statistical analysis was performed with the SPSS® program, version 24 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means and standard deviation, and categorical variables as absolute and relative frequencies. For the comparison of groups, an independent Student t-test was used, and for categorical variables, Pearson's chi-square test or Fisher's exact test. For survival analysis, the Kaplan-Meier test was used together with the log-rank test. In addition, a multivariate analysis was carried out using Cox proportional risks to estimate the hazard ratio with 95% confidence intervals for the variables of interest (overall survival and progression-free survival) adjusting the data for variables potentially predictive of mortality. A degree of significance ($p < 0.05$) was considered statistically significant.

Results

A total of 303 breast cancer cases were observed. Regarding the IHC subtype, 69.6% of patients were HR(+) and HER2(-), 17.5% HR(+)/HER2(+), 7.6% triple negative, HR(-)/HER2(-), and 5.3% were HER2(+). Median age in the study groups ranged from 51 to 56 years ($p > 0.30$). Among the clinical variables, a larger proportion of locally advanced stages was observed (IIB, IIIA, IIIB and IIIC) in comparison with early stages (I and IIA) and metastatic disease (IV) in all study groups, without significant differences being found ($p = 0.30$). Regarding the type of treatment received, statistically significant differences ($p > 0.001$) were observed between study groups in hormone therapy, with a larger proportion in the HR(+)/HER2(-) group ($n = 174$) in comparison with the HR(+)/HER2(+) ($n = 51$), HER2(+) ($n = 4$) and HR(-)/HER2(-) ($n = 7$) groups, as well as in surgical therapy ($p = 0.01$) in the HR(+)/HER2(-) group ($n = 194$) in comparison with the HR(+)/HER2(+) ($n = 50$), HER2(+) ($n = 15$) and HR(-)/HER2(-) ($n = 20$) groups. The remaining variables did not show significant differences (Table 1).

Table 2 shows non-adjusted risks for overall survival in relation to age, clinical stage, type of treatment and subtypes by IHC; in the latter, a hazard ratio (HR) = 3, (95% CI: 1.4-6.3; $p < 0.01$) and $HR = 2.3$ (95% CI: 1.07-5.2; $p = 0.03$) were observed in the HR(-)/HER2(-) and HER2(+) groups, respectively. Subsequently,

Table 1. Study population demographic, clinical and treatment characteristics

Variable	HR(+)/HER2(-) n = 211 (69.6%)	HR(+)/HER2(+) n = 53 (17.5%)	HER2(+) n = 16 (5.3%)	HR(-)/HER2(-) n = 23 (7.6%)	P
Age, years	53 (46-62)	52 (45.5-58.5)	51.5 (44.2-56)	56 (43-63)	0.31
Clinical stage, n (%)					
I, IIA	77 (36.4)	22 (41.5)	3 (18.7)	6 (26.1)	0.30
IIB, IIIA, IIIB, IIIC	97 (45.9)	25 (47.1)	11 (68.5)	12 (52.1)	
IV	19 (9)	1 (1.8)	1 (6.2)	1 (4.3)	
Positive lymph nodes (number)	1 (0-5)	1 (0-4)	5.5 (3.7-9.2)	1.5 (0-4.25)	0.06
Tumor size (mm)	30 (15-45)	30 (16.5-47.7)	36.5 (25-57.5)	42.5 (34-62.5)	0.001
Type of treatment, n (%)					
Hormone therapy	174 (82.5)	41 (77.4)	4 (25)	7 (30.4)	< 0.001
Surgery	194 (91.9)	50 (94.3)	15 (93.8)	20 (87)	0.69
Chemotherapy	181 (85.5)	47 (88.7)	15 (93.8)	23 (100)	0.01
Overall survival (months)	39 (20.5-62.7)	42 (25.5-65)	42 (13.7-67.7)	26 (11-78)	0.28

Continuous variables are presented as medians and percentiles (p25-p75) and categorical variables as frequencies and percentages (n and %).

HR(+): positive hormone receptors; HR(-): negative hormone receptors; HER2: human epidermal growth factor receptor 2.

Table 2. Non-adjusted Cox proportional risks for overall survival and recurrence/progression-free survival in women with breast cancer

Variable	Overall survival			Recurrence/progression-free survival		
	HR n = 303	95% CI	p	HR n = 270	95% CI	P
Subtypes by IHC						
HR(+)/HER2(-)	1	---	---	1	---	---
HR(+)/HER2(+)	0.79	0.36-1.7	0.56	1.1	0.5-2	0.94
HER2(+)	2.3	1.07-5.2	0.03	1.8	0.8-4	0.12
HR(-)/HER2(-)	3	1.4-6.3	< 0.01	2	0.9-4.4	0.06
Age (years)	1.01	0.98-1.03	0.32	0.99	0.96-1	0.56
Clinical stage (%)						
I, IIA	1	---	---	1	---	---
IIB, IIIA, IIIB, IIIC	6.5	2.3-18.6	< 0.01	4.9	2.2-11	< 0.01
IV	30	10-89.7	< 0.01	19.3	5.5-67.8	< 0.01
Type of treatment						
Hormone therapy	0.40	0.23-0.70	< 0.01	0.5	0.3-0.9	0.03
Surgery	0.13	0.07-0.14	< 0.01	0.13	0.06-0.28	< 0.01
Chemotherapy	1.2	0.49-3.1	0.64	1.7	0.5-5.5	0.36

Variables are presented as non-adjusted hazard ratios (HR) and 95% confidence intervals.

HR(+): positive hormone receptors; HR(-): negative hormone receptors; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry.

these risks were adjusted (Table 3) for age, clinical stage and type of treatment, where the hazard ratio of the HR(-)/HER2(-) group showed an increase (HR: 3.7; 95% CI: 1.3-10.3; p = 0.01). In addition, survival curves were plotted according to the IHC subtypes (log-rank < 0.01) (Fig. 1).

Table 2 shows the non-adjusted risks for recurrence/progression-free survival in relation to age, clinical stage, type of treatment and subtypes by IHC. In the latter, a HR = 2 was observed (95% CI: 0.9-4.4; p = 0.06) in the HR(-)/HER2(-) group. Subsequently,

said risk was adjusted for age, clinical stage and type of treatment (Table 3).

Discussion

Our results show overall survival differences in patients with breast cancer by immunohistochemical subtype. We observed that patients with HR(+) breast cancer are more common, who present with significantly smaller tumor size and lower number of positive lymph nodes, which is a reflection of a less aggressive

Table 3. Adjusted Cox proportional hazards for overall survival and recurrence/progression-free survival in women with breast cancer

	Overall survival			Recurrence/progression-free survival		
	HR n = 303	95% CI	p	HR n = 270	95% CI	p
Crude						
Subtypes by IHC						
HR (+) /HER2 (-)	1	---	---	1	---	---
HR (+) /HER2(+)	0.79	0.36-1.7	0.56	1.1	0.5-2	0.94
HER2(+)	2.3	1.07-5.2	0.03	1.8	0.8-4	0.12
HR (-) /HER2 (-)	3	1.4-6.3	< 0.01	2	0.9-4.4	0.06
Adjusted						
Subtypes by IHC						
HR (+) /HER2(-)	1	---	---	1	---	---
HR (+) /HER2 (+)	1.1	0.49-2.8	0.70	1.2	0.5-2.6	0.64
HER2(+)	1.5	0.53-4.3	0.42	1.3	0.4-3.4	0.59
HR (-) /HER2 (-)	3.7	1.3-10.3	0.01	1.6	0.6-4.7	0.32

Variables are presented as risk ratios (HR) adjusted for age, clinical stage, treatment with chemotherapy, treatment with surgery and treatment with hormone therapy, with the corresponding 95% confidence intervals (CI).

HR(+): positive hormone receptors; HR(-): negative hormone receptors; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry.

Figure 1. Overall survival Kaplan-Meier curves according to breast cancer subtypes by IHC.

HR(+)/HER2(-)

HR(+)/HER2(+)

HR(-)/HER2(+)

HR(-)/HER2(-)

Follow-up months

biological behavior and therefore of longer overall survival. In contrast, patients with breast cancer with a triple-negative subtype, which although less common, have larger tumors at diagnosis and a poorer prognosis, with shorter overall survival (adjusted HR: 3.7; 95% CI: 1.3-10.3).

In studies with European, Asian and United States populations, similar results to ours are observed, with a higher proportion of patients with HR(+) and better overall survival in this subgroup of patients. However, our proportion of HER2(+) patients, with or without positive HR, was higher, with 25% in comparison with

17% or less reported by them¹³⁻¹⁸. Historically, patients with HER2(+) had a poor prognosis⁹, but with the advances in targeted therapies for this subtype of breast cancer, similar survival rates to those of the HR(+)/HER2(-) group have been reached¹⁹. In addition, there is a contrast in the percentage of patients with locally advanced disease, which in our study is larger than 50% of cases in comparison with less than 20% observed in developed countries^{13-15,17}.

Regarding other studies in the Mexican population, the largest study reported is in a cohort of patients covered by *Seguro Popular*²⁰, where out of 4,300 women, 60.7% were HR(+)/HER2(-) and had a better prognosis in comparison with women with triple-negative breast cancer with a HR=2.16 (95% CI: 1.69-2.75). The frequency of HER2(+)breast cancer is similar to ours, with 23% and, similarly, advanced stages of the disease are more common.

One study in a hospital of the Mexican Institute of Social Security (IMSS – *Instituto Mexicano del Seguro Social*) conducted by Pérez-Rodríguez²¹ reported a proportion of luminal A breast cancer of 65% and 12% for luminal B, which is consistent with our results, with luminal subtypes with HR expression being the most common; however, the proportion of triple-negative disease of 14% was larger than that reported by us, which was 7.6%. The differences in overall survival reported in this study were similar to those observed by us, which were larger in those patients who expressed HR in comparison with those not expressing HR.

This is the first study to describe the characteristics and associated survival of breast cancer different subtypes determined by IHC in ISSSTE female beneficiaries, which adds important information together with studies on *Seguro Popular* and IMSS populations, which allows having a more complete picture of the reality of this disease in Mexico. Breast cancer is a curable disease if it is diagnosed at early stages, and it is therefore essential for the screening, diagnosis and referral programs of these patients to be improved, in order to reduce the frequency of cases detected at advanced stages of the disease, which continue to be most common in our population.

The main weakness of our study is that the sample is small and derived from a tertiary care referral hospital, and thus patient selection bias does not allow extrapolating the results to the situation of the entire institute. Breast cancer IHC subtypes allow molecular classification to be approached by means of the genomic signatures described by Perou et al.⁶. The use of IHC is considered a standard in the approach to breast cancer, as it provides way for addressing breast cancer molecular subtypes; however access to the genomic signatures necessary for molecular classification is limited, and the use of IHC in routine practice is therefore essential^{12,13}.

In conclusion, the highest proportion of women with breast cancer in our population of beneficiaries have an IHC subtype with hormone receptor expression and this group of patients has better overall survival in comparison with triple-negative patients. The development of new therapeutic options for this poor prognosis group is essential, looking to achieve an impact such as that which has been achieved in HER2-positive patients.

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