ORIGINAL ARTICLE

Poor survival in triple negative breast cancer

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RESUMEN

Antecedentes. El cáncer de mama triple negativo (TNBC) se refiere a la ausencia de expresión de los receptores de estrógeno, receptores de progesterona y receptor del factor de crecimiento epidérmico humano-2. Esta identificación ayuda a determinar el pronóstico y el tratamiento del cáncer de mama. **Objetivo.** Determinar la prevalencia de pacientes con cáncer de mama triple negativo en nuestra institución y determinar la supervivencia en comparación con los pacientes con cáncer de mama no triple negativo (NTNBC). **Material y métodos.** Se trata de un estudio retrospectivo de los casos registrados entre enero de 1995 y diciembre de 2014. El análisis incluyó a las mujeres diagnosticados con cáncer de mama invasivo, de quienes se obtuvieron datos clínicos, patológicos e inmunohistoquímicos. Se comparó la supervivencia entre los pacientes con cáncer de mama triple negativo y no triple negativo. **Resultados.** Se incluyeron 534 pacientes, entre las que la prevalencia de TNBC fue de 16.1% La supervivencia global media fue de 131 meses (IC 95%, 8.4-13.4) en el grupo TNBC, mientras que entre las pacientes NTNBC fue de 160.3 meses (IC 95%, 11.6-15,1), p = 0,0007. **Conclusión**. En nuestra población, la prevalencia del TNBC fue menor que lo reportado en otros países y regiones de México. La supervivencia del TNBC es menor que en los casos de NTNBC.

Palabras clave. Receptores. Estrógeno. Receptores. Progesterona. Receptor. ErbB-2. Neoplasias de la mama triple negativas. México.

ABSTRACT

Background. Triple negative breast cancer (TNBC) refers to the absence of expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor-2. This identification helps to determine prognosis and treatment of breast cancer. The aim of this work was to determine the prevalence of triple negative breast cancer patients in our institution and to determine survival compared to non-triple negative breast cancer patients. **Material and methods.** It is a retrospective study from clinical records between January 1995 and December 2014. Our analysis included women who were diagnosed with invasive breast cancer, from whom we obtained clinical, pathologic and immunohistochemical variables. Survival between triple negative breast cancer patients and non-triple negative breast cancer (NTNBC) patients was compared. **Results.** In total, 534 patients with a breast cancer diagnosis were included. TNBC was diagnosed in 16.1% of patients. Median overall survival (OSR) was 131 months in TNBC (95% CI, 8.4-13.4), and 160.3 months in NTNBC (95% CI, 11.6-15.1, P = 0.0007). **Conclusion.** Prevalence of TNBC was lower in our population than reported in other countries and in other Mexican population. TNBC patients have lower survival rates than NTNBC patients.

Key words. Receptors. Estrogen. Receptors. Progesterone. Receptor. ErbB-2. Triple negative breast neoplasms. Mexico.

INTRODUCTION

Breast cancer is one of the leading causes of death among Latin-American women. In Mexico, according to Instituto Nacional de Estadística y Geografía, in 2013 breast cancer was the second cause of disease mortality in women over 20 years; in 2014, incidence of breast cancer is higher in women 60-64 years.[1]

Different histological subtypes of breast cancer are described and, depends on hormonal receptors status, whether estrogen receptors (ER) and progesterone receptors (PR) are negative or positive; and if there is amplification of human epidermal growth factor receptor 2 (HER2). Triple negative breast cancer (TNBC) is defined as the absence of expression of ER, PR and HER2. This classification is very important because this helps to determine prognosis and treatment.[2] Also, it has been demonstrated that some HER2 positive tumors can develop Trastuzumab resistance and transformation from HER2 positive tumors to TNBC, this is associated with the PTEN (fosfatidilinositol-3,4,5-trisfosfato 3-fosfatasa) inactivation and worse prognosis.[3] Some of the most important risk factors

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for breast cancer development are: previous history of a mammary gland disease; first degree relatives with breast cancer; age over 40; and early menarche.[4]

TNBC has demonstrated to be a more aggressive than other subtypes, and higher incidence of metastatic disease, as well as poor survival. TNBC has shown a higher risk of recurrence, specially during the first 3 years after a surgical procedure and an increase in mortality rate after 5 years; and a quick evolution from progression to death.[2] Unfortunately, there are no target therapies in TNBC and even though, the use of chemotherapy shows a good response, patients with TNBC have a 4-fold increased risk of distant metastasis.[5] This is why chemotherapy continues to be the best option against TNBC. The aim of this work was to determine the prevalence of triple negative breast cancer patients in our institution and to determine survival compared to non-triple negative breast cancer patients.

MATERIAL AND METHODS

This is a retrospective study from patients with Breast Cancer diagnosis treated at Medica Sur Hospital Oncology Center, between January 1995 and December 2014. Our analysis included women who were diagnosed with invasive breast cancer, from whom we obtained the following data: age at diagnosis, histological type; ER, PR and HER2-neu status.

We reviewed clinical records from Medica Sur Center Oncologic Center, and tumor samples were examined and classified, hormone receptor and HER2 status was determinate by immunohystochemical analysis by the Department of Anatomic Pathology.

We obtained hormone receptor status by immunohistochemical analyses of formalin-fixed, paraffin-embedded tissue sections from incisional biopsies or mastectomies that were used for diagnosis. We determined ER and PR expression levels by using immunoperoxidase staining (Dako, Glostrup, Denmark) and quantified them with image analysis (Biogenex, San Ramon, Calif); values < 5% were categorized as negative. HER2 expression was determined by immunohistochemistry (Dako). To be characterized as HER2-positive for this study, tumors (primary or metastatic) were required to have either v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ErbB2) gene amplification, as measured by fluorescence *in situ* hybridization (Vysis, Des Plaines, Ill), or ErbB2 protein overexpression, as measured by immunohistochemistry.[3] (HercepTest;Dako). One breast cancer pathologist re-evaluated all immunohistochemical results in each sample. If HER2 status was indeterminate, analysis was made by fluorescence *in situ* hybridization.

For descriptive purposes, continuous variables were summarized as arithmetic means with standard deviations (SDs) and medians with ranges, and categorical variables were summarized as relative frequencies, proportions, and 95% confidence intervals (CIs). Inferential comparisons were performed with the Student *t* test or the Mann-Whitney *U* test according to distribution (normal or non-normal) determined by the Kolmogorov-Smirnov test. Pearson χ^2 tests and odds ratios (ORs) were used to compare the clinical and pathologic variables of TNBC.

Progression free survival (PFS) durations were measured from the date of breast surgery to the date of locoregional or systemic recurrence, for patients with stage I, II, and III TNBC. Median overall survival (OS) duration was defined as the period from the date of diagnosis to the date of death or last follow-up. PFS, and OS were analyzed with the Kaplan- Meier method, and comparisons among subgroups were performed with the log-rank test or the Breslow test. All variables were dichotomized for survival analysis. Adjustment of potential confounders was carried out with Cox proportional hazards regression analysis. All tests were 2-sided, and significance was set at $P < 0.05$. SPSS software (version 17.0; SPSS, Chicago, Ill) was used for data analysis.

RESULTS

A total of 534 patients with breast cancer diagnosis were included in this study. The median age at diagnosis was

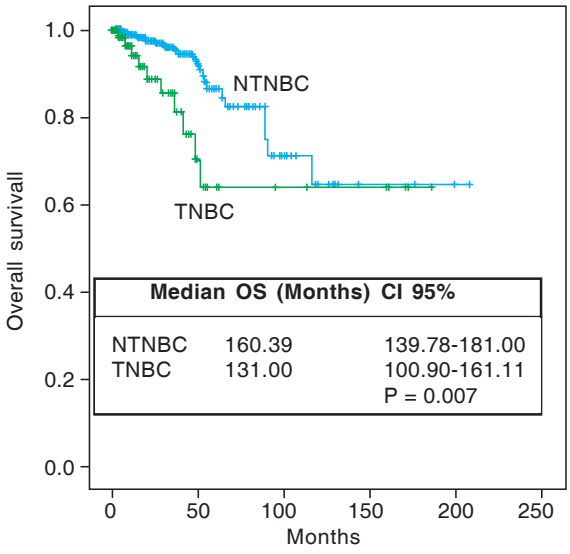

Figure 1. Overall survival in triple negative breast cancer *vs.* non-triple negative breast cancer.

54.4 ± 13.2 years (range from 24 to 91 years). The most frequent histology was Ductal carcinoma (69.1%) followed by lobular carcinoma (20%). TNBC was present in 16.1% of patients (86 patients). From the NTNBC patients 72.6% had positivity for RE, 66.5% for RP, 27.6% for HER2 and 1.7% where indeterminate. OS was 131 months in TNBC (95% CI, 100.9-161.1), and 160.3 months in non-TNBC (95% CI, 139.7-181.8, P = 0.0007) (Figure 1); PFSin TNBC was 33.13 months (CI 95%, 19.6-46.6) and in non-TNBC 37.5 months (CI 95%, 28.6-46.3, P = 0.5). The 5-year survival rate was 64% in TNBC and 86.7% in non-TNBC.

DISCUSSION

The prevalence of TNBC in Medica Sur is lower compared to other Mexican institutions such as Instituto Nacional de Cancerología (INCan), where in a study showed a prevalence of 23.1%.[6] The difference in statistics between, not just Hispanic and non-Hispanic population, but, even between Hispanic population in a public and private institution might be related to the socioeconomic level, specially because this can influence in screening programs or treatment strategies. A Chinese study included 1,578 patients from which 322 patients (20.41%) had TNBC. This patients were not just associated with a lower FPS or OS, but they showed as well a relationship between TNBC and higher ratio of breast diagnosis in young patients (< 35 years), family history of breast cancer, larger tumor size, positive lymph nodes, and a higher histological grade.[7]

After studying the genetic expression of TNBC tumors, there have been identified up to 7 molecular subtypes for TNBC; this are: Basal-Like 1 (BL1), Basal-Like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mensenchymal stem-like (MSL), luminal androgen receptor (LMR) and unstable (UNS); this is important because different types of chemotherapy had different response to each molecular subtype of tumor, for example, Paclitaxel or Docetaxel had better response in BL1/BL2 tumors compared with M o LAR tumors.[8]

It has been demonstrated that there are different risk factors for TNBC development, such as younger age at diagnosis, multiparity or young age at first pregnancy.[9] Also, breast cancer associated with BRCA mutations have higher TNBC rates.[2]

Taxane based chemotherapy in TNBC has demonstrated to have a better response.[2] Some studies have shown that the use of cisplatin as a neoadjuvant therapy has higher rates of complete pathological response in those patients that have BRCA1 mutation.[10]

Even though there is no approved target therapy for TNBC approved by the FDA, TNBC tumors have over expression of vascular endothelial growth factor (VEFG), and because of that, it has been tested the effects of some monoclonal anti-VEFG antibody such as Bevacizumab, which has shown, in addition to Paclitaxel, to increase progression free survival from 5.9 to 11.8 months in this type of patients.[11] Endothelial growth factor receptor (EGFR) target therapy in overexpressed tumors has been investigated, but studies have not shown successful results.[5] Another target therapy that has shown promising outcome is the poly-ADP-ribose polymerase (PARP) inhibitors, but they only work with patients with BRAC1 mutation. Another alternative to Neoadjuvant Chemotherapy is combination with Docetaxel and Cyclophospamide, which has shown 50% of pathological complete response in patients with TNBC; this was a better response than the one shown in other subtypes of breast cancer (0% in Luminal A-like and 4.3% in Luminal B-like).[12]

The limitation of this work is mainly the selection bias. We concluded that TNBC was less prevalent in our institution than other studies in Mexico. Patients with TNBC have worst outcomes than patients with NTNBC.

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