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Research Article

Vitamin D Deficiency and Tumor Response Failure in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy at a Medical Center in Mexico

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ABSTRACT

Background: Vitamin D deficiency has been associated with not achieving a complete pathological response in patients with breast cancer after neoadjuvant chemotherapy. The objective of this study was to determine whether vitamin D deficiency is associated with tumor response failure in patients with breast cancer operated and who received neoadjuvant chemotherapy.

Materials and Methods: This was a prospective, cross-sectional, analytical and observational study. Vitamin D was measured in patients with breast cancer who had received neoadjuvant chemotherapy and its association with tumor response was determined. For the inferential analysis, the Student's t-test, chi-square test, and Fisher's exact test were used. A p value <0.05 was considered statistically significant.

Results: Thirty-six patients were included. There was tumor response failure to treatment in 69.3% and vitamin D deficiency occurred in 58.3%. No association was found between vitamin D deficiency and tumor response failure (p = 0.729), histological type (p = 0.691), molecular profile (p = 0.969), clinical stage (p = 0.468) or menopause status (p = 0.701).

Conclusion: Vitamin D deficiency is not associated with tumor response failure in breast cancer patients who received neoadjuvant chemotherapy.

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Introduction

Breast cancer is the most frequent neoplasm worldwide; its incidence has increased from 2006 to 2015 by 0.4% per year. Only in the United States of America, the expected mortality for 2019 exceeds 47 thousand cases [1]. In Mexico, most patients are diagnosed in a locally advanced stage where neoadjuvant treatment is indicated to achieve a higher pathological response rate at the time of surgery [2]. Prospective and randomized trials have shown that the clinical response rates to neoadjuvant therapy are approximately 69%. However, the pathological complete response (pCR) ranges from 17.7 to 20.9% [3, 4]. Patients who achieve pCR have longer overall survival and disease-free survival than patients with residual invasive cancer, in addition to increasing eligibility for conservative surgeries [5-7]. Vitamin D may interfere in carcinogenesis, suppresses the expression of key molecules involved in

the regulation of the cell cycle, participates in the repair of antioxidants and DNA damage, has anti-inflammatory and antiproliferative effects, inhibits mitogenic signaling and induces apoptosis, so its importance in various types of neoplasia is a topic of current research [8, 9].

Decreased vitamin D levels have been found in patients with breast cancer at diagnosis, associated with more aggressive phenotypes and metastatic disease [10-12]. Although with controversial results, some studies have found that vitamin D deficiency is associated with the possibility of not achieving pCR after neoadjuvant treatment [13, 14]. The objective of this study was to investigate the association between vitamin D deficiency and tumor response failure in patients with locally advanced breast cancer operated and who received neoadjuvant chemotherapy.

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Materials and Methods

I Study Design and Participants

This was a prospective, cross-sectional, analytical and observational study conducted in the High Specialty Medical Unit No. 25 of the Instituto Mexicano del Seguro Social in Monterrey, Nuevo León, Mexico. Patients included were over 18 years old, with locally advanced breast cancer, anatomical clinical stage IIA to IIIC, who had completed neoadjuvant treatment and before surgery, or who had undergone curative breast surgery with neoadjuvant treatment prior. Patients were excluded if they had carcinoma *in situ*, metastatic or recurrent disease, or with any disease that, secondarily, could interfere with vitamin D metabolism. Demographic and pathological information included age, weight, height, menopause status, comorbid, histological pattern of the tumor, molecular profile based on the expression of the hormonal receptor (HR) and overexpression of the human epidermal growth factor receptor 2 (HER2), clinical stage, vitamin D deficiency, which was defined as the serum level <20 ng / ml, and tumor response failure, which was defined as the absence of pCR based on the eighth edition of the American Joint Committee on Cancer guidelines [15]. With prior authorization, blood sample was taken from each patient to determine vitamin D level.

II Blood Sample and Laboratory Evaluation

The blood was taken with a range of no more than 2 months if it was before surgery or up to 3 months if it was after the surgical procedure. The blood sample was protected from light and stored at a temperature of 2 to 8°C. For its analysis, 2 ml of serum was required. Vitamin D level

was measured using the chemiluminescence method. The insufficient sample had hemolysis, marked lipemia, or had an incorrect identification and packaging was rejected.

III Statistical Analysis

For the numerical variables, descriptive statistics were used. The dimensional variables with normal distribution were reported with median and range, while for the nominal variables, they were reported with percentage. Concerning inferential statistics, the Student's t-test was used to compare independent variables with normal distribution, chi-square test or Fisher's exact test was used to recognize the association between categorical variables and compare proportions. A p value <0.05 was considered statistically significant. The IBM SPSS Statistics version 23.0 software was used to organize and analyze the information that was collected.

Results

Between December 2018 and November 2019, 36 patients were included in this study, with a median age of 55 years (range 34-71). Vitamin D deficiency was registered at 58.3%, the minimum serum value recorded was 8.04 ng / ml and the maximum value was 25.7 ng / ml. The tumor response failure to neoadjuvant treatment was 69.3%. The clinical and pathological characteristics of the 36 patients were classified based on vitamin D level (Table 1). The association between vitamin D deficiency and tumor response failure (p = 0.729), histological type (p = 0.691), molecular profile (p = 0.969), clinical-stage (p = 0.468) and the status of menopause (p = 0.701) were determined.

Table 1: Clinical and pathological characteristics of 36 breast cancer patients classified based on vitamin D level.

	Total (n=36)	Vitamin D level		p
		<20 ng / ml (n=21)	≥20 ng / ml (n=15)	
Age (years)	55 (34-71)	53 (34-66)	55 (43-71)	0.267
Weight (kg)	74.8 (49-122)	75 (62-103)	67 (49-122)	0.476
Size (m)	1.55 (1.47-1.70)	1.55 (1.47-1.70)	1.56 (1.49-1.70)	0.793
Tumor response failure	25 (69.3%)	14 (38.8%)	11 (30.5%)	0.729
Menopause ^a	23 (69.6%)	13 (39.3%)	10 (30.3%)	0.701
Histological type				0.691
Ductal	25 (69.3%)	15 (41.6%)	10 (27.7%)	
Lobular	5 (13.8%)	2 (5.5%)	3 (8.3%)	
Other	4 (11%)	2 (5.5%)	2 (5.5%)	
Unknown	2 (5.5%)	2 (5.5%)	0	
Molecular profile				0.969
HR+/HER2-	15 (41.6%)	9 (25%)	6 (16.6%)	
HR+/HER2+	5 (13.8%)	3 (8.3%)	2 (5.5%)	
HR-/HER2+	6 (16.6%)	3 (8.3%)	3 (8.3%)	
Triple-negative	8 (22.1%)	5 (13.8%)	3 (8.3%)	
Unknown	2 (5.4%)	1 (2.7%)	1 (2.7%)	
Clinical stage				0.468
II	10 (27.7%)	7 (19.4%)	3 (8.3%)	
III	26 (72.1%)	14 (38.8%)	12 (33.3%)	

Data are presented in median (range) or absolute frequency (percentage).

HR: Hormonal Receptor; HER2: Human Epidermal growth factor Receptor 2.

^aIn the analysis of this data, three patients were not included.

Most patients received anthracycline and taxane-based chemotherapy, sequentially completing eight cycles of treatment. Modified radical mastectomy was performed in 35 patients and only one patient underwent conservative breast surgery. Ductal histology was 69.3% of the tumors, 13.8% lobular and 11% other histology, which included mucinous and papillary carcinoma. At diagnosis, 27.7% of the patients were in clinical stage II, while 72.1% were in clinical stage III. The molecular profile based on the expression of HR and overexpression of HER2 was 41.6%, 13.8%, 16.6% and 22.1% for HR + / HER2-, HR + / HER +, HR- / HER + and triple-negative, respectively.

Discussion

Although with controversial results, some investigations have found an association between vitamin D deficiency and the probability of not reaching pCR [13, 14]. In the present study, the association between vitamin D deficiency and tumor response failure in patients with breast cancer who received neoadjuvant chemotherapy was evaluated. In this study, no association between vitamin D level and tumor response was found. Nevertheless, the frequency of patients with vitamin D deficiency was higher than reported worldwide, which could be secondary to a lower nutritional contribution of vitamin D in the Mexican population living in the north of the country and that the blood sample was taken at the end of the neoadjuvant treatment and not a diagnosis [13-16]. This strategy was carried out because there are studies that have observed that chemotherapy can lower the vitamin D level, so the authors considered taking the blood sample at the end of the neoadjuvant treatment to know the vitamin D level closer to surgery and to be able to relate it to the tumor response [17, 18]. Another aspect to take into account is that, although the collection of patient data was carried out for a year, the climatic station at diagnosis and the total hours per day that the patients were exposed to sunlight were not registered. These factors could have intervened independently in the modification of the vitamin D level and the response to the cancer treatment, probably conditioning the study to be negative [19, 20].

No association was found between vitamin D deficiency and histological type, molecular profile and clinical stage, unlike other studies where it has been found the association with more aggressive phenotypes with higher histological grade, not luminal, greater axillary involvement, higher cell proliferation, and metastatic disease [11, 12]. This could be due to the small number of patients included in the investigation, the heterogeneity of clinical and pathological characteristics of the patients and no metastatic disease were included. Although patients with papillary and mucinous carcinoma with sufficient vitamin D levels were registered, which could be related to the good prognosis of these histologies, this association cannot be asserted due to the small number of patients [21]. Neither was found an association between the vitamin D level and menopause. This could be due to a possible modification of the effect by individual factors such as the body mass index and alcoholism, which were not studied in the recruited population and which could have influenced menopausal patients, in addition to polymorphisms of the vitamin D receptor gene that could intervene in the development and prognosis of breast cancer [10, 22-25].

At diagnosis, 72.1% of patients were in clinical stage III, which could represent the delay in diagnosis and treatment, whether due to fear of the

patient or difficulties in going to a health center. Most patients received anthracycline and taxane-based chemotherapy, sequentially completing eight cycles of treatment. For administrative reasons, no patient received anti-HER neoadjuvant treatment for overexpressed HER cancer. Although several patients received neoadjuvant hormonal treatment, they did not accept the surgery or follow-up was lost, so they were not included in this investigation. The pCR achieved in this study was greater than that recorded worldwide. However, this did not determine the surgical option of conservative breast surgeries. Although the justification of the surgeon for not performing the procedure is not known, several factors could have intervened, such as the traditional opinion that conservative surgery could have a higher recurrence rate, the delay in treatment with postoperative radiotherapy, difficulties in obtaining a transoperative pathological report to determine the surgical margin, socioeconomic level and place of residence of the patient and the absence of tumor marking prior to the start of neoadjuvant treatment [2, 4, 26, 27].

The limitations of the study were the small number of patients, the heterogeneity in their clinical and pathological characteristics, and the lack of other variables that could have intervened in the result. Studies with a larger population and follow-up are required, with a more specific group of patients, for example, excluding patients with luminal breast cancer and HER2+ breast cancer that have not received neoadjuvant anti-HER therapy, since they are the least responsive to neoadjuvant chemotherapy [13].

Conclusion

In conclusion, vitamin D deficiency is not associated with tumor response failure in breast cancer patients who received neoadjuvant chemotherapy. However, the time in the disease natural history and specific patient characteristics will have to be explored more deeply to determine the importance of vitamin D in breast cancer. pCR is a prognostic factor for both overall survival and disease-free survival, so the search for modifiable biomarkers that intervene in the tumor response is essential in patients with breast cancer.

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Ethical Approval

The study was approved by the Monterrey, Nuevo León IMSS Ethics Board (IRB No: R-2019-1901-046). This research complied with the standards recognized by the Helsinki Declaration.

Consent

All participants gave their written consent for inclusion in the study.

Conflicts of Interest

None.

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