Clinical Neurology and Neurosurgery 173 (2018) 61–64

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Diagnosis of brain metastases in breast cancer patients resulting from neurological symptoms

Bernardo Cacho-Díaz[a,*], Héctor Spínola-Maroño[a], Victor A. Arrieta[a], Martin Granados-García[b], Talia Wegman-Ostrosky[c], Laura G. Mendoza-Olivas[b], Mariana Chávez-MacGregor[d]

[a] Neuro-Oncology Unit, National Cancer Institute, Mexico
[b] Head and Neck Department, National Cancer Institute, Mexico
[c] Research Division, National Cancer Institute, Mexico
[d] Health Services Research, Breast Medical Oncology Departments at the University of Texas MD Anderson Cancer Center, Mexico

ARTICLE INFO

Keywords:
Metastatic breast cancer
Neuro-oncology
Central nervous system metastases
Neurological symptoms

ABSTRACT

Objectives: Breast cancer (BC) is the leading cause of morbidity and mortality. Neurological symptoms are highly feared because they are associated with central nervous system metastases (CNSm). So, we aimed to analyze the association of neurological symptoms with CNSm.

Patients & Methods: Patients with BC referred for a neuro-oncological evaluation at a cancer referral center from June 2012 to December 2017 were included. Demographic, oncological history, comorbidities, clinical symptoms and signs, and their correlation with CNSm were prospectively acquired during consultation in a computerized database. Analyses included descriptive observations, bivariate, and logistic linear regression tests that compared associations.

Results: A total of 857 patients with BC were referred for assessment. The most frequently occurring symptoms included headache, focal motor weakness, focal-sensitive complaints, and visual complaints. Of the 1029 neuro-oncology diagnoses made, the most common were CNSm, primary headache, and chemotherapy-induced neuropathy. The risk factors associated with CNSm in patients with neurological symptoms were HER2+, younger age at cancer diagnosis, presence of extracranial metastases, and > 1 neurological symptom (mainly headache: hazard ratio (HR), 2.1 [95% confidence interval (CI), 1.5–2.7]; visual complaints: HR, 2.3 (95%CI, 1.2–4.2); and ataxia: HR, 2.1 (95%CI,1.04–4.3).

Conclusions: Clinical symptoms and cancer characteristics were correlated with the development of CNSm. Specific risk and protective factors were identified.

Among BC patients with neurological symptoms, CNSm should always be considered, especially in patients with certain oncological and clinical features.

1. Introduction

Breast cancer (BC) is one of the most common cancers worldwide according to reports from GLOBOCAN 2012 [1] and The American Cancer Society [2]. Neurological symptoms are one of the most common causes of consultation [3] and one of the most feared complications among oncological patients [4]. Central nervous system metastases (CNSm) are associated with important neurological symptoms and usually lead to poor prognoses. BC is the second most common cause of CNSm, and although the incidence of CNSm has not been exactly determined [5], the frequency in one autopsy series was approximately 30% [6]. Improved imaging techniques and screening protocols are facilitating and improving diagnosis.

There is a broad spectrum of possible neurological symptoms in BC patients, including pre-treatment symptoms, injuries associated with the use of chemotherapy or radiotherapy, and those due to CNSm. To our knowledge, there are no previous reports that have related clinical symptoms to the diagnosis of CNSm. Therefore, we designed this study to describe neurological symptoms in BC patients and to determine if there is an association with the final neuro-oncological diagnosis, mainly CNSm.

* Corresponding author at: Neuro-oncology Unit, Instituto Nacional de Cancerología, Av San Fernando 22, Col. Sección XVI, Mexico City, ZC14,080, Mexico.
E-mail address: bernardocacho@doctor.com (B. Cacho-Díaz).

https://doi.org/10.1016/j.clineuro.2018.08.002
Received 28 June 2018; Received in revised form 21 July 2018; Accepted 1 August 2018
Available online 02 August 2018
0303-8467/

2. Materials and methods

From June 2012 to December 2017, the Neuro-oncology Unit personnel prospectively acquired information during consultations directly from patients and clinical records. The collection of clinical, imaging, and pathological data was performed in a pre-formatted computerized database to avoid operator-dependent variation in the data. The main author supervised all information entry.

The inclusion criteria used were patients with BC diagnosed by a certified pathologist from our institution, aged ≥18 years, and seen in the outpatient clinic or as inpatient consultation during hospitalization by a neuro-oncology specialist with any neurological symptom considered relevant by their attending oncologist. The exclusion criteria were incomplete clinical records and absence of pathological confirmation of BC.

For the purpose of this study, luminal A (LumA) was considered when estrogen receptors (ER) were positive (ER+), progesterone receptors (PR) were positive (PR–), and human epidermal growth factor receptor (HER2 Neu) was negative (HER2–); luminal B HER2+ (Lum B HER2+) was considered if ER/PR + and HER2+ were present; luminal B HER2– (Lum B HER2–) was considered if RE/RP + HER2 Neu– plus Ki67 > 20%; HER2+ was considered if RE/RP– and HER2+ and triple negative for ER/PR/HER– were present, all of which were determined by using immunochemical techniques. A comorbid condition was diagnosed if the patient had diabetes, hypertension, hyperlipidemia, and/or was overweight/obese. Diabetes was diagnosed according to the American Diabetes Association criteria [7], hypertension as suggested by the Eighth Joint National Committee [8], hyperlipidemia was diagnosed when at least two high blood levels of total cholesterol and/or triglycerides were observed, and patients were considered to be overweight if body mass index (BMI) was 25–29 and to be obese if BMI ≥30.

If the patient had clinical symptoms considered by the neuro-oncology specialist to be compatible with CNSm, contrast-enhanced magnetic resonance imaging (MRI) would be performed. If there was no clinical suggestion of CNSm or MRI results were negative, the patients were followed for ≥18 months to be sure the neurological symptoms were not associated with CNSm. All CNSm cases were diagnosed on the basis of clinical and MRI findings.

The Institutional Ethics and Research Committees approved all interventions (INCAN/CI/837/17). Student's *t*-test and the Mann–Whitney U-tests were used to compare two continuous variables. We used linear logistic regression to compare > 3 variables, the hazard ratio (HR) to compare prognostic observations with a 95% confidence interval (95%CI), and a P value < 0.05 was considered as indicative of statistical significance.

3. Results

A total of 857 patients with BC were referred for neuro-oncological assessment; 856 were women (99.9%), and the median ages at the time of cancer diagnosis and at the time of neuro-oncological consultation were 50 years and 55 years, respectively. Table 1 describes the general characteristics of the patients. Comorbidities were found in 71% of the patients, the most common being overweight/obesity in 53%, followed by hypertension, diabetes, and hyperlipidemia. The main reasons for consultation involved one symptom in 589 (57%) patients, more than one in 382 (37%) patients, and 58 were asymptomatic (6%). The most common symptoms reported were headache, focal motor weakness, focal-sensitive complaints, and visual complaints, including diplopia, ptosis, and altered vision. Overall, 1029 neuro-oncological diagnoses were made; the most common were CNSm, primary headache, and chemotherapy-induced neuropathy. Other diagnoses included syncope, mild cognitive impairment, psychiatric illness, sleep disorders, peripheral vertigo, Bell´s palsy, and additional neurological conditions not related to cancer or its treatment. The neurological symptoms are presented in Table 2, and the neuro-oncological diagnoses are presented in Table 3. Symptoms that led to the diagnosis of CNSm and their oncological status were compared with those who did not have CNSm. The mean follow-up after neuro-oncological diagnosis was 73.6 months (IQR, 40–91), and the median survival after CNSm diagnosis was 7 months (95% CI, 5.3–8.7 months).

Table 4 presents the results from the bivariate analysis. A positive association with CNSm was found for patients with BC who were HER2+, triple negative, RE–, RP–, had extra-cranial disease, and had > 1 neurological symptom. The primary neurological symptoms were headache (HR, 2; 95%CI, 1.5–2.7), focal motor weakness (HR, 2.1;

Table 1
General characteristics of 857 patients referred for neuro-oncological consultation.

Median age at time of cancer diagnosis	50 years
Median age at time of NO consultation	55 years
Cancer subtype	n (%)
Luminal A	276 (32)
Luminal B/HER2+	115 (13)
Luminal B/HER2–	108 (13)
HER2+	96 (11)
Triple negative (Basal)	137 (16)
Not available	125 (15)
Comorbidity	606 (71)
Diabetes	180 (21)
Hypertension	256 (30)
Hyperlipidemia	108 (13)
Overweight	225 (26)
Obesity	238 (28)

Table 2
Neurological complaints in 857 breast cancer patients.

Symptom/Sign	No. (%)
Headache	370 (36)
Focal motor weakness	178 (17)
Focal-sensitive deficit	179 (17)
Visual complaint, including diplopia	123 (12)
Seizure(s)	108 (11)
Altered mental status	99 (9.6)
Cranial neuropathy	94 (9)
Appendicular ataxia	82 (8)
Vertigo	82 (8)
Abnormal movements	65 (6)
Cognitive complaint	62 (6)
Vertebral/radicular pain	60 (6)
Nausea/vomit	53 (5)

Table 3
Neuro-oncological diagnoses in 857 breast cancer patients.

Diagnosis	Patients with neuro-oncological diagnosis No. (%)*
Central nervous system metastases	259 (25)
Primary headache	195 (19)
Other**	175 (17)
Chemotherapy-induced neuropathy	132 (13)
Vertebral/epidural metastases	70 (7)
Cerebrovascular disease	60 (6)
Epilepsy (non-tumor related)	41 (4)
Degenerative dementia	32 (3)
Skull metastases	23 (2)
Degenerative spine disease	22 (2)
Paraneoplastic disease	11 (1)
Delirium	9 (1)
TOTAL	1029 (100%)

* 172 patients had more than one diagnosis.

** Includes syncope, peripheral vertigo, psychiatric illness, sleep disorders, Bell´s palsy, etc.