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Original article

A prospective study on the neurological complications of breast cancer and its treatment: Updated analysis three years after cancer diagnosis

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ABSTRACT

Objectives: To quantify the prevalence of neurological complications among breast cancer patients at one and three years after diagnosis, and to identify factors associated with neuropathic pain (NP) and chemotherapy-induced peripheral neuropathy (CIPN).
Material and methods: Prospective cohort study including 475 patients with newly diagnosed breast cancer, recruited among those proposed for surgical treatment (Portuguese Institute of Oncology, Porto). Patients underwent a neurological evaluation and had their cognitive function assesses with the Montreal Cognitive Assessment, before treatment and at one and three years after enrollment. We estimated the prevalence of each neurological complication, and odds ratios (OR), adjusted for socio-demographic and clinical characteristics, to identify factors associated with NP and CIPN.
Results: More than half of the patients [54.7%, 95% confidence interval (95%CI): 50.2–59.2] presented at least one neurological complication, at one or at three years after cancer diagnosis. Between the first and the third year of follow-up, there was an increase in the prevalence of NP (from 21.1% to 23.6%), cognitive impairment (from 7.2% to 8.2%), cerebrovascular disease (from 0.6% to 1.5%) and brain metastasis (from 0.0% to 0.6%). The prevalence of CIPN decreased from 14.1% to 12.6%. Axillary lymph node dissection was associated with NP at one year (OR = 2.75, 95%CI: 1.34–5.63) and chemotherapy with NP at three years (OR = 2.10, 95%CI: 1.20–3.67). Taxane-based chemotherapy was strongly associated with prevalence of CIPN at one and three years.
Conclusion: Neurological complications are frequent even three years after cancer diagnosis and NP remained the major contributor to the burden of these conditions among survivors.

Introduction

Breast cancer is the most frequent cancer among women, estimated to have accounted for approximately one quarter of all cases of cancer diagnosed in 2012 [1]. Access to early diagnosis through mammography screening and effective treatments [2] makes breast cancer one of those with a better prognosis. The 5-year net survival is now greater than 80% in most developed countries [3], and this translates into a high number of women living for longer periods with possible sequelae of breast cancer and its treatment, emphasizing the relevance of a comprehensive study of the burden of cancer among survivors.

Neurological complications, either direct, namely metastatic disease, or due to indirect mechanisms, including vascular disorders, paraneoplastic syndromes or side-effects of treatments, may be a frequent source of morbidity among breast cancer patients [4,5]. We previously followed a cohort of breast cancer patients during the first year after diagnosis, and showed that nearly half of the women treated for breast cancer had at least one neuro-oncological complication and one quarter developed at least two during this period; the most frequent were neuropathic pain (NP) and chemotherapy-induced peripheral neuropathy (CIPN) [6].

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The progression of cancer itself and the subsequent exposure to additional treatments, the late and/or cumulative effects of some options of cancer management, but also the possibility of recovering from some of the neuro-oncological complications over time, bring attention to the importance of a comprehensive assessment of the prevalence of these conditions in the long term. Therefore, we updated the follow-up of this cohort up to three years after diagnosis, aiming to quantify the prevalence of neurological complications among breast cancer patients, and to identify factors associated with NP and CIPN.

Material and methods

We conducted a prospective study with newly diagnosed breast cancer women, followed for three years. The study protocol has been described in detail elsewhere [7].

Patients and setting

Patients proposed for surgery were consecutively recruited in 2012, among those admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal. We excluded women that had received any treatment for breast cancer before, those previously treated with chemotherapy and/or radiotherapy in the chest and/or axillary areas for other primary cancers, and those considered less likely to be able to cooperate due to cognitive impairment [score lower than 17, or lower than 16 for women over 65 years, in the Montreal Cognitive Assessment (MoCA) [8,9]].

The cohort included 506 patients with incident breast cancer, from whom 31 were lost to follow-up until the three-year of follow-up (11 patients died, 10 abandoned the study, six could not be contacted, two were transferred to another hospital and two were considered unable to cooperate by the neurologist). Therefore, a total of 475 (93.9%) completed the three-year follow-up evaluation with a median [percentile 25-percentile 75 (P25-P75)] time of follow-up of 1095 (1073–1126) days and were included in the present analysis. The patients lost to follow-up were not significantly different (participants vs. lost to follow-up) regarding age (median: 54.7 vs. 58.1 years, $p = 0.130$), education [median: 6 vs. 4 schooling years (4–6), $p = 0.081$] and cancer stage (stage 0/I: 53.9% vs. 48.4%, $p = 0.581$).

Data collection

All participants underwent a neurological evaluation at baseline (before any treatment) and at one and three years after enrollment.

Complementary exams (e.g.: computed tomography, magnetic resonance imaging, nerve conducting studies) were requested whenever indicated, according to the usual practice of the hospital. In all evaluations, socio-demographic data were collected using a structured questionnaire and clinical records were reviewed for cancer stage, breast cancer treatments and the presence of recurrence. Cancer stage was classified according to the American Joint Committee on Cancer staging manual [10].

Prevalence of neurological complications

Neurological complications affecting the patients at one and three years after cancer diagnosis were recorded; this included conditions identified *de novo* in any of these follow-up evaluations or diagnosed before, but still present at the follow-up evaluation.

CIPN was defined as peripheral neuropathy occurring after chemotherapy. Among subjects with peripheral neuropathy at baseline, CIPN was considered present only if there was a worsening of the preexisting neuropathy. The severity of CIPN was quantified using the Total Neuropathy Score, clinical version (TNSc) (range: 0 to 28) [11] and the Common Terminology Criteria for Adverse Events, V.4.0 (CTCAE) (range: 1 to 5) [12]. In both scales, higher scores represent greater severity.

NP was considered probable, according to the International Association for the Study of Pain (IASP) [13], if pain distribution was neuroanatomically plausible and history was suggestive of relevant lesions or diseases affecting the somatosensory system, plus negative or positive sensory signs in neurological examination, confined to the innervation territory of the injured nervous structure. Pain sensation and light touch sensation were assessed using a wood cocktail stick and a piece of cotton wool, respectively, as recommended by the IASP [13]. We considered NP secondary to breast cancer treatments as prevalent in each of the evaluations if it was present in the last 24 h, in the breast, chest wall, axilla, or medial upper arm on the affected side, donor region of breast reconstruction, or in the hands/feet (secondary to CIPN). In order to quantify pain severity, the severity subscale of the Brief Pain Inventory Short Form was used [14]; it consists of a mean score of four questions measuring the worst, least, average and current pain in the past 24 h (range: 0 to 10, with 0 = “no pain” and 10 = “pain as bad as you can imagine”).

Among patients submitted to mastectomy, phantom breast syndrome was defined as the presence of the sensation that the removed breast is still present [15]. When in addition, patients described a sensation of pain in the removed breast, phantom breast pain was considered present [15] and the CTCAE was used to grade phantom pain (range: 1 to 5) [12].

Cognitive impairment was considered present when the patients' MoCA score (range: 0 to 30) was at least 2.0 standard deviations below age- and education-adjusted cut-offs for possible cognitive impairment [8].

Statistical analysis

Patients' characteristics were presented as counts and proportions for all categorical variables, and median and P25-P75 for quantitative variables.

Prevalence estimates and corresponding 95% confidence intervals (95%CI) were estimated for each of the neurological complications at one and three years after cancer diagnosis. The McNemar's test was used to compare the proportion of patients with each complication at one and three years.

Adjusted odds ratios (OR) and 95%CI were computed using logistic regression, to quantify the relation between sociodemographic and clinical characteristics of the patients and the presence of NP and CIPN at one and three years after cancer diagnosis.

Statistical analyses were conducted using STATA®, version 11.2 (StataCorp, College Station, TX, USA).

Results

Patients' characteristics

At baseline, half of the women had less than 55 years of age and more than two thirds had less than 10 years of education. A total of 6.5% were diagnosed with non-invasive breast cancer (ductal carcinoma in situ) and the remaining with invasive breast cancer stage I (47.4%), II (30.7%), III (14.7%) or IV (0.6%).

The breast cancer treatments performed during the first year after diagnosis are presented in Table 1. Nearly half of the patients were submitted to mastectomy and just over one third to axillary lymph node dissection (ALND). Most of the participants underwent adjuvant treatment. Docetaxel-based regimens were used by more than two thirds of women receiving chemotherapy.