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Original article

Neurological complications of breast cancer: A prospective cohort study

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ABSTRACT

Objectives: Neurological complications secondary to breast cancer treatment may be an important contributor to these patients morbidity. We aimed to quantify the incidence of neurological complications of breast cancer treatment during the first year after diagnosis.
Materials and methods: We performed a prospective cohort study with 506 patients recruited at the Portuguese Institute of Oncology of Porto, among those newly diagnosed. Participants underwent a neurological examination before treatment, after surgery, after chemotherapy (whenever applicable) and at one year after enrollment. The Montreal Cognitive Assessment was used to assess cognitive function, at baseline and at one year. We computed one-year cumulative incidence estimates and the corresponding 95% confidence intervals (95%CI) for each of the neurological complications.
Results: Just over half of women had breast cancer stage 0 or I. A total of 6.9% were submitted to neoadjuvant chemotherapy but most of them completed adjuvant treatment – endocrine therapy, radiotherapy or chemotherapy (83.9%, 73.0% and 52.5%, respectively). The cumulative incidence of at least one oncological-related neurological complication during the first year after diagnosis was 48.4% (95%CI: 44.1–52.8); the most frequent were neuropathic pain (30.8%, 95%CI: 27.0–35.0), chemotherapy-induced peripheral neuropathy (16.8%, 95%CI: 13.8–20.3), phantom breast pain/syndrome (16.6%, 95%CI: 13.6–20.1) and cognitive decline (8.1%, 95%CI: 5.8–11.1).
Conclusions: Neurological complications were a frequent side-effect of breast cancer management in the first year after diagnosis, especially neuropathic pain and chemotherapy-induced peripheral neuropathy. Accurate diagnosis and treatment of these complications are important to minimize the burden associated with breast cancer treatment in breast cancer survivors.

Introduction

Breast cancer is the most common tumor and the leading cause of cancer death in women worldwide, with an estimated 1.7 million new cases diagnosed in 2012, corresponding to 25% of all cancers among women [1]. The improvement in breast cancer survival (the 5-year relative survival is higher than 80% in most of the more developed countries [2,3]), as a result of earlier diagnosis and advances in cancer management [4], along with the expected overdiagnosis and overtreatment associated with breast cancer screening [5], highlights the need for an exhaustive assessment of the burden of breast cancer, including treatments' side-effects.

Cancer may affect the nervous system through direct (*e.g.*: metastatic disease) or indirect effects. The latter comprise treatment side-effects, such as chemotherapy-induced peripheral neuropathy (CIPN), neuropathic pain (NP), cognitive decline, abnormal immune responses to cancer, leading to paraneoplastic syndromes, or coagulation disorders, which result in cerebrovascular disease [6,7].

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Neurological complications of cancer and neurological side-effects of cancer management can occur in approximately half of the breast cancer patients [8–10], and may cause symptoms more disabling than cancer itself [7]. Early diagnosis and aggressive treatment of these conditions can ameliorate neurological symptoms and substantially improve patients' quality of life [7].

To our knowledge, previous studies providing a comprehensive assessment of the incidence of neurological complications in cancer patients did not address specifically breast cancer and may not reflect the state of the art of cancer diagnosis and treatment [11–13]. Therefore, we aimed to quantify the incidence of neurological complications of breast cancer treatment, during the first year after diagnosis, using a contemporary cohort of women in earlier stages of disease, followed prospectively.

Materials and methods

We conducted a prospective cohort study of 506 women consecutively recruited in 2012 among those admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal, with newly diagnosed breast cancer. The study methodology has been described in detail elsewhere [14]. Briefly, we selected women proposed for surgery whose follow-up would go on in same hospital. We excluded those previously treated for cancer, submitted to breast surgery, and those scoring less than 17, or less than 16 for women over 65 years old, in the Montreal Cognitive Assessment (MoCA), which was assumed to correspond to a high probability of cognitive impairment [15].

All participants underwent a neurological examination at baseline (before any treatment), two weeks after surgery, three weeks after chemotherapy (if applicable), and at one year after enrollment. The MoCA [16,17] was used at baseline and at one year, to assess cognitive function; we used the normative data of the MoCA scores in the Portuguese population to define the age- and education-specific mean minus 1.5 standard deviations (SD) as cut-off points for possible cognitive impairment [15].

Neurological examinations were conducted by experienced neuro-oncology neurologists, according to the usual practice of the hospital. The systematic evaluations conducted at baseline and at one year later comprised the assessment of cognitive functions, cranial nerves, muscular strength, sensory function, reflexes, Babinski signal, gait and coordination. Neurologic examinations were conducted after surgery and chemotherapy, aiming to identify NP and CIPN. Complementary exams (*e.g.*: computed tomography, magnetic resonance imaging, nerve conducting studies) were requested whenever indicated.

NP was considered probable, according to the criteria proposed by Treede et al. [18] and by the European Federation of Neurological Societies guidelines on NP assessment [19], if pain had a distinct neuroanatomically plausible distribution and history was suggestive of relevant lesion or disease affecting the peripheral or central somatosensory system, plus negative or positive sensory signs in neurological examination, confined to innervations territory of the damaged nervous structure. CIPN was defined as neuropathy newly diagnosed or worsening after chemotherapy. Phantom pain was defined according to the Common Terminology Criteria for Adverse Events, V.4.0 (CTCAE) [20], as a disorder characterized by marked discomfort related to a limb or an organ that has been removed from the body; in accordance with this definition, we considered phantom breast pain present when a sensation of pain in a removed breast was described by the patients after mastectomy. Phantom breast syndrome was considered present in patients with only non-painful phantom breast sensation.

The CTCAE [20] was used to grade the severity of CIPN and phantom breast pain and the Brief Pain Inventory Short Form (BPI-SF) [21,22] to quantify the pain intensity in last 24 h, for NP and phantom breast pain.

Prevalent neurological disorders at baseline were identified during the initial neurological assessment or by patients' self-report. In the latter, the diagnosis was confirmed by the neurologist and written clinical information was requested when patients were followed for these conditions in another institution.

Incident cases of neurological complications during the first year after enrollment are identified through referral by any member of the clinical team, or during the systematic neurological evaluations; date of onset was estimated based on information provided by the patients. We considered that patients had cognitive decline when the MoCA scores decreased to values below the established cut-offs for possible cognitive impairment during follow-up. We computed cumulative incidence estimates and the corresponding 95% confidence intervals (95%CI) for each of the neurological complications at 12 months of follow-up. Kaplan–Meier failure estimates curves for the first year of follow-up were calculated for NP and CIPN. Statistical analysis was conducted using STATA®, version 11.2 (StataCorp, College Station, TX, USA).

Results

Fig. 1 depicts the number of patients in each evaluations performed. A total of 503 participants completed the one-year follow-up evaluation.

Patient characteristics

At baseline, 35.2% of the women were less than 50 years old [mean (standard deviation): 55.2 (11.2)], 60.9% had less than nine years of schooling [mean (standard deviation): 7.7 (4.5)] and one-quarter were retired (24.7%). Half of the participants were from districts other than the district of Porto (50.4%).

The main clinical features of the participants and their treatments are presented in Table 1. Just over half were diagnosed breast cancer at stage 0 or I. Only 6.9% were submitted to neoadjuvant chemotherapy but most of them went on to adjuvant treatment – endocrine therapy, radiotherapy or chemotherapy (83.9%, 73.0% and 52.5% respectively). Among those submitted to chemotherapy, the most frequent scheme was FEC-D [three cycles of concomitant 5-fluorouracil (5-FU) 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 followed by three cycles of docetaxel 100 mg/m^2]. Overall, 71.6% of the patients submitted to chemotherapy performed a taxane-based scheme. Around half of the patients were submitted to mastectomy and approximately one-third underwent axillary lymph node dissection.

Neurological conditions at baseline

The most prevalent neurological conditions at baseline were migraine (8.3%, 95%CI: 6.2–11.0, from which 14.3%, 95%CI: 6.3–28.2 had aura), postural tremor (4.3%, 95%CI: 2.9–6.5), neurological sequelae of other pathologies (1.8%, 95%CI 0.9–3.4), tension-type headache (1.8%, 95%CI: 0.9–3.4), carpal tunnel syndrome (1.2%, 95%CI: 0.5–2.6) and polyneuropathy (1.0%, 95%CI: 0.4–2.4). Cerebrovascular disease, epilepsy, trigeminal neuralgia, Parkinson's disease and restless leg syndrome were each present in less than 1% of the patients.

Most women with migraine at baseline were less than 50 years old (67.5%). During the first year after diagnosis, one of these patients had an increase in the frequency of migraine and required prescription for migraine prophylaxis, while the remaining reported a lower frequency.