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Original article

Variation in type of adjuvant chemotherapy received among patients with stage I breast cancer: A multi-institutional Portuguese cohort study

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ABSTRACT

Background: A contemporary US study showed an increase in the use of chemotherapy in the last decade for some patients with stage-I breast cancer; with a rise in more intensive regimens, and declining use of anthracyclines. Nevertheless, there is still uncertainty on the absolute benefit of chemotherapy for these patients and the optimal regimen. In this study we compare those findings with the patterns of care among a Portuguese cohort of stage-I breast cancers.

Methods: Retrospective cohort study of patients with stage-I breast cancer diagnosed from 2006 to 2008 at four Portuguese institutions. The use and type of chemotherapy was evaluated.

Results: Among patients with stage I–III breast cancer 39.4% (n = 682) had stage I disease. Of the 595 eligible patients, 22.4% were treated with chemotherapy, 33.9% aged <55 years vs. 12.7% aged >65 years ($p < 0.001$). Thirteen percent of patients with hormone receptor (HR)+/HER2− tumors, 52.7% of patients with HER2+ and 66.0% of patients with HR-/HER2− received chemotherapy ($p < 0.001$). In addition, we found inter-institutional variability, with the use of chemotherapy ranging from 0.0% to 43.4% ($p < 0.001$). Eighty-five percent of patients treated with chemotherapy received less-intensive regimens with anthracycline-based regimens, such as doxorubicin and cyclophosphamide, being the most frequently used, while docetaxel and cyclophosphamide was only used in 1.5% of cases.

Conclusions: Overall, almost one-quarter of patients received chemotherapy with institutional variability. When treated, mostly less-intensive associations including anthracyclines were used, which contrasts with contemporary US practice. This study highlights the need for health-services research to understand local practices and tailor quality improvement interventions.

Introduction

Breast cancer is the most common female cancer in Europe [1]. In the western world, a substantial minority of these patients are diagnosed with stage I breast cancer, which is, overall, associated with excellent outcomes [2–10]. As an example, in one large series

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of patients with stage I tumors, the 10-year breast cancer specific death was ≤12% for T1a-bN0 tumors and it was ≤16% for T1cN0 tumors not treated with adjuvant chemotherapy [3].

Several recent studies have reported prognostic estimates tailored to clinicopathological features such as tumor subtype, grade and size allowing physicians to better define who should be treated with chemotherapy and in whom we can safely avoid this treatment [2,4,11]. Given that stage I patients were consistently under-represented in most adjuvant chemotherapy clinical trials to date, there is still uncertainty on their best adjuvant treatment, and population based studies can provide valuable insights on treatment selection in such patients.

Recently, a retrospective study performed in academic United States (US) institutions showed that around one third of stage I patients received adjuvant chemotherapy, a practice that increased over the last decade, particularly for patients with human epidermal growth factor-2 (HER2)-positive (+) and hormone receptor (HR)-negative (−)/HER2− tumors while remaining stable for patients with HR+ tumors [2,12]. In addition, an increase in use of more intensive regimens, such as anthracycline and taxane based therapies was also found. Furthermore, among less intensive chemotherapy regimens, rise in the use of taxane-based regimens such as docetaxel and cyclophosphamide (TC) and decrease in the use of anthracyclines (e.g. doxorubicin and cyclophosphamide [AC]) was noted [12].

Until recently, there has been lack of detailed multi-institutional Portuguese data focused on breast cancer patients. In 2014, several Portuguese Institutions, both public and private, started to collect granular information on clinicopathological features, patterns of care and clinical outcomes of their patients with breast cancer. This collection evolved from recovering retrospective data to starting prospective collection of data using a national cancer registry platform. In this study we report the patterns of chemotherapy use among patients with stage I breast cancer diagnosed from 2006 to 2008 and treated at participating institutions.

Methods

Study design and data source

This was a retrospective cohort study. Patients were included if they received at least part of their treatment at the reporting center. Four centers contributed with data: Instituto Português de Oncologia de Lisboa Francisco Gentil (a public referral cancer center), Centro Hospitalar de Lisboa Norte (a public hospital and an academic center), Hospitais CUF Lisboa (a private hospital) and Hospital da Luz (a private hospital). Patient chart, pathology and pharmacy reports were reviewed. The Cancer Registry of Southern Portugal (*Registo Oncológico Regional do Sul* [ROR-Sul]) platform was used for this study. All centers adhered to the same data collection procedures and to the variables definitions previously developed by ROR-Sul. Data audits were performed to assure data quality. The audits focused on 10% of the cases and all variables had a higher than 95% concordance rate across all variables and all centers. Institutional review boards (IRBs) from participating centers, the ROR-Sul direction and ROR-Sul review board approved the study protocol.

We identified women with a first invasive Stage I–III breast cancer diagnosed in 2006–2008 (N = 1730). We only included 682 (39.4%) patients with pathological Stage I disease. We then excluded women treated with neoadjuvant chemotherapy, unknown adjuvant chemotherapy regimen or unknown HR/HER2 status. Therefore, a final analytic cohort of 595 patients with stage I breast cancer was identified (Fig. 1).

Outcomes variables

The primary outcome of this study was treatment with adjuvant chemotherapy (yes/no) for stage I breast cancer. Secondary outcome was type of chemotherapy (non-intensive regimen/intensive regimen; grouped according to supplemental Fig. A.1). The database has information on treatment/drug administered abstracted by chart review.

Key variables

Covariates included age at diagnosis (<55, 55–65, ≥65), treatment center (A, B, C, D), year of diagnosis (2006, 2007, 2008), tumor size (T1a: > 0.1–0.5 cm, T1b: >0.5–1 cm, T1c: >1.0–2 cm), tumor grade (grade 1, 2, 3, unknown), tumor immunophenotype using immunohistochemical (IHC) tests for estrogen receptor (ER) and progesterone receptor (PR), as well as IHC, in-situ hybridization (ISH) or copy number tests for HER2 over-expression or amplification (HR+/HER2−, HER2+ and HR-/HER2−; ER or PR were positive if expressed by ≥ 1% of tumor cells; HR was defined as positive if ER or PR were positive and negative if ER and PR were negative; HER2 was defined as positive if IHC 3+ or ISH with HER2/CEP17 ratio > 2.2 or HER2 > 6 copies), and histological type according to WHO classification of breast tumors (invasive ductal carcinoma/no special type, invasive lobular carcinoma or other/unknown).

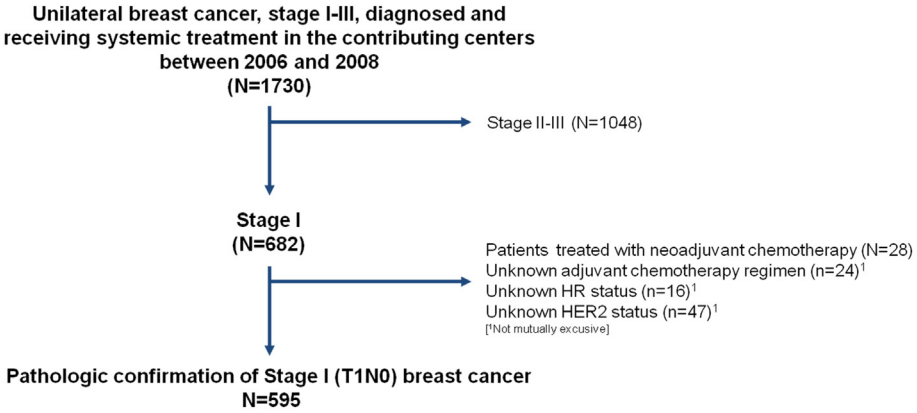

Fig. 1. Flow diagram of patient population. HR: Hormone receptor; HER2: Human epidermal growth factor 2.