The Breast 37 (2018) 107–113

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Treatment adoption and relative effectiveness of aromatase inhibitors compared to tamoxifen in early breast cancer: A multi-institutional observational study

Arlindo R. Ferreira [a, b], Ana Palha [a], Lurdes Correia [a], Pedro Filipe [a], Vasco Rodrigues [a], Ana Miranda [c], Rosário André [c], João Fernandes [d], Joaquim Gouveia [d], José L. Passos-Coelho [e], António Moreira [f], Margarida Brito [f], Joana Ribeiro [g], Otto Metzger-Filho [h], Nancy U. Lin [h], Luís Costa [a, b], Inês Vaz-Luis [i, h, *]

[a] Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Av. Prof. Egas Moniz, 1649-035 Lisbon, Portugal
[b] Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-035 Lisbon, Portugal
[c] Registo Oncológico Regional do Sul, Instituto Português de Oncologia F. G. de Lisboa, R. Prof. Lima Basto, 1099-023 Lisbon, Portugal
[d] Hospitais CUF Lisboa, R. Mário Botas, 1998-018 Lisbon, Portugal
[e] Hospital da Luz, Avenida Lusíada, 100, 1500-650 Lisbon, Portugal
[f] Instituto Português de Oncologia F. G. de Lisboa, R. Prof. Lima Basto, 1099-023 Lisbon, Portugal
[g] Fundação Champalimaud, Av. Brasília, 1400-038 Lisbon, Portugal
[h] Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA
[i] Institut Gustave Roussy, Unit INSERM 981, 114 Rue Edouard Vaillant, 94800 Villejuif, France

ARTICLE INFO

Article history:
Received 12 June 2017
Received in revised form
18 October 2017
Accepted 3 November 2017

Keywords:
Early breast cancer
Aromatase inhibitors
Tamoxifen
Treatment effectiveness

ABSTRACT

Background: Since 2005, aromatase inhibitors (AIs) have been the adjuvant treatment of choice for postmenopausal women with early breast cancer (BC). In this study we characterize the adoption of AIs in Portugal, variables associated with treatment administration, and compare its effectiveness (either in monotherapy or sequential therapy) to tamoxifen monotherapy (TAM).

Patients and methods: This was a retrospective cohort study that included postmenopausal women with stage I-III hormone receptor (HR) positive BC diagnosed from 2006 to 2008 and treated with adjuvant endocrine therapy in four participating institutions.

Results: Of the 1283 eligible patients, 527 (41%) received an AI (16% as monotherapy, 25% as sequential therapy) and 756 (59%) TAM. Patients treated with AI had less differentiated tumors, with higher TNM stage, and were more frequently HER2-positive. Use of AI also differed by center (use range from 33% to 75%, $p < 0.001$). With a median follow-up of 6.3 years and controlling for clinicopathological and treatment characteristics, treatment with AI had a better overall survival (OS) when compared with TAM (adjusted-HR 0.55, 95% CI 0.37–0.81).

Conclusion: AIs were successfully introduced as adjuvant treatment for HR-positive BC in Portuguese hospitals. Its use was influenced by tumor and patient characteristics, but also center of care. In this large cohort, AI use was associated with an OS benefit.

1. Introduction

In developed countries, the majority of breast cancers (>80%) are diagnosed in early stages, and can be treated with curative intent [1]. Of these, more than 2/3 are hormone receptor-positive [2], for whom the prognosis is substantially improved by adjuvant endocrine therapy (ET). As compared to no endocrine therapy, adjuvant ET is associated with a reduction in the rates of disease recurrence of approximately 50%, and this translates into a reduction in breast cancer mortality of more than 1/3 in the first 15 years after diagnosis [3]. Since 2005, international guidelines have supported several adjuvant ET regimens for postmenopausal patients,

* Corresponding author. Department of Medicine and Unit INSERM 981, Institut Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France.
E-mail address: Ines-Maria.Vaz-Duarte-Luis@gustaveroussy.fr (I. Vaz-Luis).

https://doi.org/10.1016/j.breast.2017.11.003
0960-9776/

including tamoxifen (TAM), aromatase inhibitors (AI) or a sequence of these agents [4–6]. Nevertheless, several clinical trials showed an advantage of regimens including an AI, an effect recently summarized in a large meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that estimated a lower 10-year breast cancer mortality in the AI *vs.* TAM group (RR = 0.85, 95% CI 0.75–0.96) [7]. Therefore, given the absolute benefit of strategies with AIs, there is an overall consensus that the treatment of high risk patients, such as those with nodal involvement, high grade or high Ki-67, should include an AI [5].

Even so, the choice between different ETs also entails the choice of different safety, tolerability/adherence and cost profiles. While TAM is associated with an increased risk of thromboembolic events and endometrial cancer, AIs are associated with an increase in the risk of osteoporosis and bone fractures, as well as arthralgias and other musculoskeletal complaints [8]. Out-of-pocket and health system cost differences also exist (for example, in the United States, patients receiving AIs were more likely to experience financial hardship than those taking TAM only [9]).

Recently, a multi-institutional group of Portuguese centers, both public and private, started to collect granular information on clinicopathological features, patterns of care and clinical outcomes of their patients with breast cancer using a regional cancer registry platform [10]. In this study we characterize how real world providers introduced different ET strategies after 2005 (date of first consensus advocating the use of AI-based strategies for postmenopausal women [6]) and explore the comparative effectiveness of these interventions.

2. Patients and methods

2.1. Study design and data source

This is a retrospective cohort study. Data from four hospitals in the Lisbon area, Portugal, were retrieved from *Registo Oncológico Regional do Sul* (ROR-S; Southern Regional Oncology Registry). ROR-S is a population-based cancer registry. Data audits focused on 10% of cases were performed and variables had a higher than 95% concordance rate. Due to the observational nature of the study, treatments and follow-up were performed at patient-physician description. ROR-S institutional review board approved study protocol. Description of data collection and procedures were previously reported [10]. We followed the STROBE statement in reports of cohort studies.

2.2. Cohort definition

We selected all consecutive postmenopausal primary breast cancer patients with stage I-III disease, tumors expressing estrogen/progesterone receptor (≥1%) and diagnosed and treated systemically (i.e., treatments beyond local therapy as surgery or radiotherapy) at *Centro Hospitalar de Lisboa Norte, Hospitais CUF Lisboa, Hospital da Luz* or *Instituto Português de Oncologia Francisco Gentil de Lisboa* between 2006 and 2008. Follow-up details (treatment, new tumors and vital status) were available up to December 2013. We excluded patients who did not have surgery and patients with other concurrent primary tumors. A cohort of 1283 patients was identified (Fig. 1). Two groups were further defined as a function of type of ET received: Group A) 756 (58.9%) patients treated with TAM monotherapy and Group B) 527 (41.1%) patients treated either with AI monotherapy or sequential TAM-AI/AI-TAM. In addition to this cohort of 1283 patients (overall cohort), a landmark cohort and propensity score matching cohorts were built specifically for the effectiveness analyses as a strategy to address confounding, and the details about their set-up are elaborated in the statistical analysis section.

2.3. Variables definition

2.3.1. Outcomes

Primary outcome was overall survival (OS). OS was defined as time from diagnosis to death of any cause. Follow-up was available until up to December 2013.

2.3.2. Menopausal status

Postmenopausal was defined as older than 52 at date of diagnosis. Previous studies of unselected Portuguese women showed that the median age of menopause for the Portuguese population is 48 years (interquartile range [IQR] 44–52) [11]. Given the treatment with (neo)adjuvant chemotherapy in approximately 50% of

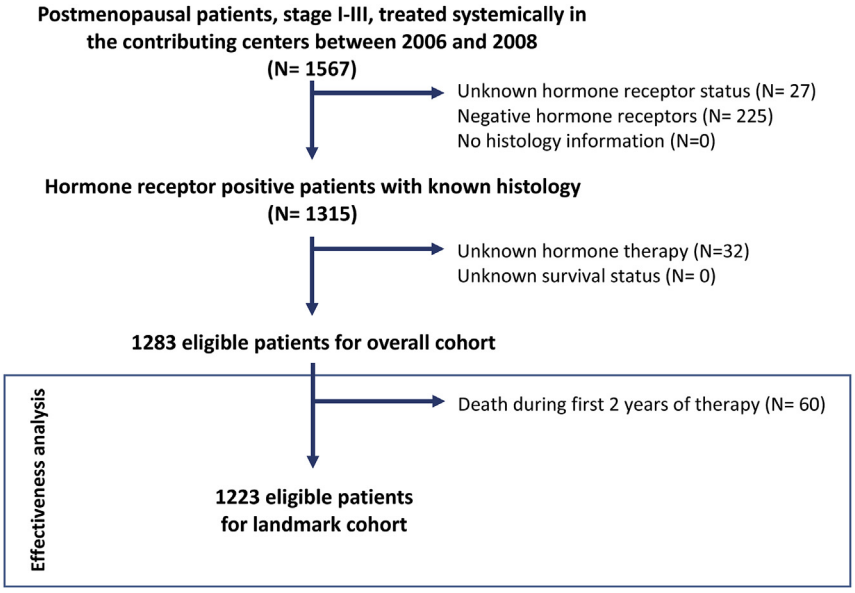

Fig. 1. Study diagram.