The Breast 28 (2016) 161–166

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Short report

Endocrine therapy for hormone treatment-naïve advanced breast cancer

Miguel Martin*, Sara Lopez-Tarruella, Yolanda Jerez Gilarranz

Medical Oncology Department, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, C/Dr Esquerdo 46, Madrid 28009, Spain

ARTICLE INFO

Article history:
Received 26 May 2016
Accepted 31 May 2016
Available online 18 June 2016

Keywords:
Advanced breast cancer
Metastatic breast cancer
Endocrine therapy
Endocrine therapy-naïve

ABSTRACT

A proportion of patients with hormone receptor-positive locally advanced or metastatic breast cancer will not have received prior endocrine therapy. However, there are limited clinical data specifically in these patients. We conducted a review of randomized phase II and III clinical studies of anastrozole, letrozole, exemestane, palbociclib, and fulvestrant to determine the evidence base supporting use of specific endocrine therapies in this patient population. From our findings, there is a paucity of clinical studies in patients with endocrine therapy-naïve disease; however, it appears that first-line treatment effects are consistent between patients who have and have not received prior endocrine treatment.

Introduction

Standard treatment for patients with localized hormone receptor-positive breast cancer, which accounts for the majority of cases at diagnosis, includes endocrine therapy. Consequently, few patients with locally advanced or metastatic disease will not have received prior endocrine therapy and may present with: (1) de novo advanced disease and have not received prior systemic treatment; (2) advanced disease and have not been treated with endocrine therapy; and (3) recurrent metastatic breast cancer and have not received treatment with adjuvant endocrine therapy.

Materials and methods

We performed a literature review of randomized studies of aromatase inhibitors (anastrozole, letrozole, and exemestane), a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib), and a selective estrogen receptor degrader (fulvestrant) to determine the level of evidence supporting the use of specific endocrine therapies in patients with locally advanced or metastatic hormone receptor-positive disease who have not received any prior endocrine therapy.

Results

Summaries of the studies identified in our literature review are presented in Table 1. Two phase III, double-blind studies of anastrozole vs. tamoxifen as first-line treatment were identified. In one study, time to progression (TTP) with anastrozole was at least equivalent to tamoxifen [1], whereas in the second study, anastrozole significantly improved TTP vs. tamoxifen [2]. However, neither study evaluated efficacy specifically in the subgroup of patients with de novo advanced breast cancer or those who were truly endocrine therapy-naïve.

The efficacy of exemestane vs. tamoxifen as first-line treatment was investigated in a phase III open-label study [3]. Progression-free survival (PFS) findings favored exemestane over tamoxifen overall and in patients who had not received prior hormonal treatment. Furthermore, exploratory analyses suggested that previous hormonal therapy was not a prognostic factor for PFS.

Several studies evaluated fulvestrant as first-line therapy. In a double-blind study, no differences in TTP between fulvestrant 250 mg (the previous recommended dose) and tamoxifen treatment were seen [4]. Furthermore, no difference was observed between patients who had received prior adjuvant tamoxifen treatment and the overall population (unpublished data).

Abbreviations: CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CI, confidence interval; ER, estrogen receptor; HER, human epidermal growth factor receptor; HR, hazard ratio; LD, loading dose; NA, not applicable; OR, objective response; OS, overall survival; PFS, progression-free survival; PgR, progesterone receptor; TTP, time to progression.

* Corresponding author.
E-mail addresses: mmartin@geicam.org (M. Martin), slopeztarruella@gmail.com (S. Lopez-Tarruella), itacayoli@hotmail.com (Y.J. Gilarranz).

http://dx.doi.org/10.1016/j.breast.2016.05.015

Table 1
Randomized clinical studies in post-menopausal patients with locally advanced or metastatic breast cancer identified in the literature review.

Study design	Patient population	Receptor status	Treatment	Endocrine therapy	Overall findings
Phase III, randomized, double-blind, multicenter study (TARGET) [1]	Post-menopausal women with locally advanced or metastatic breast cancer ($N = 668$)	Patients with hormone receptor-positive (ER+ and/or PgR+) tumors or tumors of unknown status were included HER2+ patients were not excluded ER+, PgR+: 24–26% ER+, PgR−: 8–9%	Anastrozole 1 mg vs. tamoxifen 20 mg	Patients had to be eligible for first-line treatment with endocrine therapy Prior adjuvant chemotherapy or endocrine therapy for early disease was permitted. Tamoxifen treatment was not permitted within 12 months prior to study entry 69–70% of patients had not received prior adjuvant therapy 6–9% had received prior adjuvant endocrine therapy only 3–5% had received adjuvant endocrine therapy plus cytotoxic therapy	TTP Anastrozole: 8.2 months Tamoxifen: 8.3 months (HR 0.99; lower 95% CI 0.86; 2-sided $p = 0.941$) OR Anastrozole: 32.9% Tamoxifen: 32.6% (2-sided $p = 0.787$) OS, not reported
Phase III, randomized, double-blind, multicenter study (TARGET) [2]	Post-menopausal women with locally advanced or metastatic breast cancer ($N = 353$)	Patients with hormone receptor-positive (ER+ and/or PgR+) tumors or tumors of unknown status were included HER2+ patients were not excluded ER+, PgR+: 64–67% ER+, PgR−: 17–19%	Anastrozole 1 mg vs. tamoxifen 20 mg	Patients had to be eligible for first-line treatment with endocrine therapy Prior adjuvant chemotherapy or endocrine therapy for early disease was permitted. Tamoxifen treatment was not permitted within 12 months prior to study entry 60–61% of patients had not received prior adjuvant therapy 11–12% of patients had received adjuvant endocrine therapy only 7–9% had received adjuvant endocrine therapy plus cytotoxic therapy	TTP Anastrozole: 11.1 months Tamoxifen: 5.6 months (HR 1.44; lower 95% CI 1.16; 2-sided $p = 0.005$) OR Anastrozole: 21.1% Tamoxifen: 17.0% OS, not reported
Phase III, randomized, open-label, multicenter study (EORTC) [3]	Post-menopausal women with hormone-sensitive metastatic or locally recurrent breast cancer ($N = 382$)	Primary tumors or metastases had to be hormone receptor-positive. Patients with tumors of unknown status were included HER2+ patients were not excluded ER+, PgR+: 57% ER+, PgR−: 25%	Exemestane 25 mg vs. tamoxifen 20 mg	Previous hormone therapy for metastatic breast cancer was not allowed; however, patients were permitted to have received prior treatment with adjuvant tamoxifen 42% of patients had received prior systemic therapy 10% had received prior hormonal therapy only 11% had received adjuvant endocrine therapy plus cytotoxic therapy	PFS Exemestane: 9.9 months Tamoxifen: 5.8 months (HR 0.84; 95% CI 0.67, 1.05; log-rank $p = 0.121$; Wilcoxon $p = 0.028$) OR Exemestane: 46% Tamoxifen: 31% ($p = 0.005$) OS Exemestane: 37.2 months Tamoxifen: 43.3 months (log-rank $p = 0.821$)
Randomized, double-blind, multicenter study [4]	Post-menopausal women with locally advanced or metastatic breast cancer ($N = 587$)	Patients with hormone receptor-positive (ER+ and/or PgR+) tumors or tumors of unknown status were included HER2+ patients were not excluded ER+, PgR+: 42% ER+, PgR−: 16–19%	Fulvestrant 250 mg[a] vs. tamoxifen 20 mg	Previous endocrine therapy for advanced breast cancer was not allowed No adjuvant endocrine therapy (tamoxifen) was allowed within 12 months of study entry 22–25% had received prior endocrine therapy (tamoxifen)	TTP Fulvestrant: 6.8 months Tamoxifen: 8.3 months (HR 1.18; 95% CI 0.98, 1.44; $p = 0.088$) OR Fulvestrant: 31.6% Tamoxifen: 33.9% ($p = 0.45$) OS Fulvestrant: 36.9 months Tamoxifen: 38.7 months (HR 1.29; 95% CI 1.01, 1.64; $p = 0.04$)