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Clinical predictors of benefit from fulvestrant in advanced breast cancer: A Meta-analysis of randomized controlled trials

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ABSTRACT

Background: Data on the comparative efficacy of fulvestrant and other endocrine treatments are inconsistent. Clinical markers predictive of greater benefit from fulvestrant compared to the alternate endocrine agents have not been identified.
Methods: We searched the literature from inception to May 2015, using MEDLINE, EMBASE, and major conference proceedings. We included randomized controlled trials (RCTs) that compared fulvestrant containing arm to either tamoxifen or an aromatase inhibitors (AI) and presented results for subgroup analyses as Hazard Ratios (HR) for Time to Progression (TTP) or Progression Free Survival (PFS). Subgroup analyses reported in at least two RCTs were included. Data were then weighted using generic inverse variance approach and pooled in meta-analysis using RevMan 5.3 software. Difference between subgroups was tested with chi^2 statistics.
Results: Analysis included 4 RCTs comparing fulvestrant-based therapy to AI alone and comprising 2382 patients (1190 on fulvestrant and 1192 on control arms). TTP/PFS was the primary endpoint in all included studies. Four sub-groups fulfilled our criteria. Fulvestrant was associated with greater benefit in patients with visceral metastasis (HR 0.85 vs 1.02 for no visceral disease, p for difference = 0.05) and in those patients with a time to recurrence >5 years (HR 0.80 vs 1.09 for recurrence $\leqslant$5 years, p for difference = 0.02). There was no apparent difference in benefit based on age >65 years (HR 0.86 vs 0.96, p for difference = 0.32) or HER2/neu status (HR 0.36 vs 0.92, p for difference = 0.09).
Conclusion: Patients with advanced breast cancer with visceral involvement and longer time from diagnosis to recurrence had significantly better TTP/PFS with the use of fulvestrant. These results may have implications for selection of patients in the design of future clinical trials and to inform treatment decisions in clinical practice.

Introduction

Aromatase inhibitors are currently the preferred first line therapy for postmenopausal women with estrogen receptor (ER) positive advanced breast cancer [1]. In second line setting, either tamoxifen or aromatase inhibitors are used in sequence. Fulvestrant (Faslodex, AstraZeneca), a selective estrogen receptor downregulator has gained interest because of its unique mechanistic characteristics – it has a potent ER antagonist property with no known agonist effects [2]. The Fulvestrant-ER complex is highly unstable leading to its rapid degradation, thereby causing irreversible loss of cellular ER [3].

Fulvestrant entered formal clinical testing in the 1990's and since then there have been eight phase II and III Randomized Controlled Trials (RCTs) evaluating fulvestrant or its combination against either an aromatase inhibitor or tamoxifen for treatment of advanced breast cancer. The design of studies, the dose of fulvestrant, and the results of these RCTs are inconsistent. Currently, the Food and Drug Administration (FDA) has approved fulvestrant for use in metastatic breast cancer after progression on previous endocrine treatment at a dose of 500 mg every 4 weeks, after an initial month of biweekly loading dose.

Fulvestrant has been shown to have comparable efficacy and toxicities to other endocrine therapy in most RCTs [4–9], although two other RCTs conducted in the first line setting have demonstrated a statistically significant superiority in favor of the fulvestrant

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containing treatment in terms of both overall survival and progression free survival, despite cross-over in one of the studies [10,11]. A previous meta-analysis comparing efficacy and toxicities of fulvestrant containing regimen with AI or tamoxifen showed similar overall efficacy between fulvestrant monotherapy or the addition of fulvestrant to an AI as first or second line therapy in advanced breast cancer [12]. Beyond the ER, a common marker predictive of benefit from all endocrine therapies, additional biological or clinical markers have not been identified to predict for a higher benefit from fulvestrant. In an attempt to further investigate this question, we conducted a meta-analysis of different sub-groups of patients from RCTs comparing fulvestrant or its combination with an aromatase inhibitor to either aromatase inhibitor or tamoxifen alone.

Methods

Search criteria

A comprehensive search of MEDLINE, EMBASE, and COCHRANE databases from the inception to May 2015 was performed. Key words included POPULATION: exp Breast Neoplasms/or (exp Carcinoma/and exp breast/). EXPOSURE: Fulvestrant/ or Faslodex/ selective estrogen receptor downregulator. STUDY TYPES: Randomized control trials/ or double-blind method/ or single-blind/ or clinical trials/ or comparative study/or evaluation studies/ or Follow-up studies/ or prospective studies. OUTCOMES: prognosis/or disease-free survival/or medical futility/or treatment outcome/or treatment failure/or disease progression/or morbidity/or survival rate/ or survival analysis/or disease-free survival/or proportional hazards model/or exp risk. Hand searches of the reference lists of all pertinent reviews were undertaken. Presentations made at ASCO Annual Meetings, ASCO Breast Cancer Symposium, and San Antonio Breast Cancer Symposium in the last 5 years were also searched. We included studies reporting results of RCTs that compared a fulvestrant containing arm to a non-fulvestrant containing arm for treatment of post-menopausal women with inoperable locally advanced or metastatic breast cancer. Only the studies reporting HRs for predefined sub-groups were included. Any subgroup that was reported in more than one study was included in the meta-analysis.

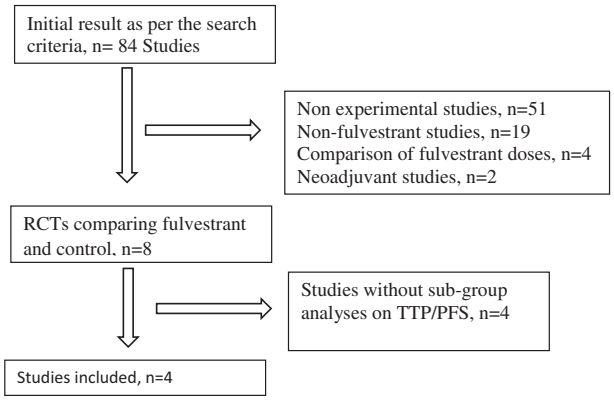

Fig. 1. PRISMA search result.

Data extraction

Data on time to event outcomes such as progression-free survival (PFS) or time-to-progression (TTP) and reported as Hazard Ratios (HR) and respective 95% Confidence Intervals (CI) were extracted for all subgroups meeting the above criteria. Data was collected by two authors independently (JG, SN), any discrepancies were resolved by consensus. For the trials that did not report outcomes according to subgroups, authors were contacted by email but we were unable to obtain any further data.

Risk of bias in the included studies was assessed using the Cochrane collaboration's tool for assessing risk of bias in RCTs [13]. Two authors (JG, SN) independently assessed each study under 5 main headings for risk of bias.

Statistical methods and analysis

Data on HR for each subgroup of patients were pooled in a meta-analysis using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of HR were pooled using DerSimonian and Laird random effect models in which the studies were weighted using the generic inverse variance approach [14]. Chi^2 statistics was used to measure the difference between subgroups and evidence of heterogeneity among studies was assessed using i^2 statistics [15]. All tests were 2-sided and statistical significance was defined as $p < 0.05$.

Results

Characteristics of the studies

Details of our search results can be seen in the PRISMA diagram (Fig. 1). We excluded 4 major RCTs [7–9,11]. In total, 4 subgroups met our inclusion criteria: age (>65 vs ⩽65 years), presence vs absence of visceral metastases, time to cancer reoccurrence from primary diagnosis (>5 vs ⩽5 years), and presence vs absence of HER2 overexpression. Number of trials reporting results according to the subgroups varied: 4 trials each reported subgroup analysis according to age, and presence of visceral metastasis, while 2 studies each reported subgroups according to time to cancer recurrence and HER2 status. The study characteristics are summarized in Table 1.

Risk of bias

None of the included studies had major flaws in assessment of their risk of bias. A common caveat however was the expected absence of blinded intervention. Detailed assessment of risk of bias is summarized in Table 2.

Sub group analyses

The fulvestrant containing arm was found to be significantly better in terms of TTP/PFS in 3 sub-groups: Age >65 years (HR 0.86, 95% CI 0.75–0.99), visceral metastasis present (HR 0.85, 95% CI 0.77–0.95), and time to recurrence >5 years (HR 0.80, 95% CI 0.66–0.96), whereas TTP/PFS didn't favor either arms in the sub-

Table 1
Study characteristics.

Study	Treatment group	Control group	*N* (Experimental)	*N* (Control)	Efficacy endpoint	Line of therapy	Age range (years)
Chia et al. 2008 [5]	Fulvestrant	Exemestane	351	342	TTP	1st/2nd/3rd	32–91
Johnston et al. 2013 [6]	Fulvestrant	Exemestane	231	249	PFS	1st/2nd	57–75
Bergh et al. 2012 [4]	Fulvestrant + anastrozole	Anastrozole	258	256	TTP	1st	33–90
Mehta et al. 2012 [10]	Fulvestrant + anastrozole	Anastrozole	350	345	PFS	1st	27–92