Original Study

Network Meta-Analysis Comparing Overall Survival for Fulvestrant 500 mg Versus Alternative Therapies for Treatment of Postmenopausal, Estrogen Receptor-Positive Advanced Breast Cancer Following Failure on Prior Endocrine Therapy

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Abstract

An overall survival (OS) network meta-analysis was conducted for fulvestrant 500 mg versus alternative therapies for postmenopausal, estrogen receptor-positive advanced breast cancer after endocrine therapy failure. The results suggested improved OS for fulvestrant 500 mg versus fulvestrant 250 mg and megestrol acetate 40 mg and similar OS (numerical advantages) to other comparators in the study.

Background: We conducted a review of randomized trials to compare the overall survival (OS) with fulvestrant 500 mg versus alternative treatment for estrogen receptor-positive advanced breast cancer following endocrine therapy failure. **Materials and Methods:** Hazard ratios (HRs) were obtained by modeling OS data with the Weibull distribution. A fixed-effect Bayesian network meta-analysis was conducted. The evidence network included anastrozole 1 mg, letrozole 2.5 mg, fulvestrant 250 mg, exemestane 25 mg, megestrol acetate 40 mg, and everolimus 10 mg plus exemestane 25 mg as comparators. Post-antiestrogen and post-aromatase inhibitor subgroup networks were analyzed. **Results:** In the overall analysis, the HRs suggested improved OS for fulvestrant 500 mg versus fulvestrant 250 mg and megestrol acetate 40 mg, and numerically favorable differences with fulvestrant 500 mg versus other comparators. In the antiestrogen subgroup, the HRs suggested improved OS for fulvestrant 500 mg versus fulvestrant 250 mg and megestrol acetate 40 mg; numerical differences in the HRs were seen versus anastrozole 1 mg and letrozole 2.5 mg. In the aromatase inhibitor subgroup, the HRs for OS numerically favored fulvestrant 500 mg versus fulvestrant 250 mg and exemestane 25 mg. **Conclusion:** Acknowledging the limitations of the present network meta-analysis, these findings suggest that fulvestrant 500 mg might provide improved OS versus fulvestrant 250 mg and megestrol acetate 40 mg for treatment of estrogen receptor-positive ABC following endocrine therapy failure. Although OS efficacy versus everolimus 10 mg plus exemestane 25 mg (for overall evidence network), anastrozole 1 mg, exemestane 25 mg, and letrozole 2.5 mg is numerically favorable, additional studies are required to draw formal conclusions.

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Introduction

For postmenopausal women with advanced breast cancer (ABC; locally advanced or metastatic) who have hormone receptor-positive tumors, hormonal therapy with an antiestrogen (AO) or aromatase inhibitor (AI) is recommended.[1,2] However, the optimal sequencing of current hormonal therapies for patients with ABC has yet to be established.

Fulvestrant is a selective estrogen receptor (ER) degrader that binds to and blocks the ER and increases ER degradation.[3] Fulvestrant is approved for the treatment of postmenopausal women with ER-positive ABC and disease progression following failure of previous AO therapy.[4,5] Fulvestrant was initially approved for use at a dose of 250 mg every 28 days; however, fulvestrant 500 mg is now the approved dose based on data from the phase III Comparison of Faslodex in Recurrent Metastatic Breast Cancer

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(CONFIRM) trial that demonstrated a significant improvement in progression-free survival (PFS) for a fulvestrant 500 mg dose regimen (fulvestrant 500 mg on days 0, 14, and 28, and every 28 days thereafter) versus fulvestrant 250 mg.[6] Fulvestrant 500 mg was also associated with greater median overall survival (OS) compared with fulvestrant 250 mg (26.4 vs. 22.3 months; hazard ratio [HR], 0.81; 95% confidence interval, 0.69-0.96; $P < .05$) in the CONFIRM trial.[7]

In the absence of direct head-to-head comparisons between hormonal therapies, indirect treatment comparisons are an accepted method of estimating relative treatment effects,[8,9] thereby informing the treatment choice and facilitating disease-management optimization. Network meta-analysis (NMA) is one such indirect treatment comparison methodology that is increasingly being used to conduct multiple treatment comparisons, particularly when large data sets are included in the analysis. By developing a network of randomized clinical trials that have ≥ 1 intervention in common, the relative efficacy of a particular intervention versus alternative interventions can be obtained indirectly by using the common comparators across the individual trials.[10]

Previous NMAs have examined the comparative effect of hormonal treatments on PFS among patients receiving treatment for ABC.[11,12] However, improvement in OS is recognized as the optimum goal of cancer treatment.[13] Therefore, the objective of the present study was to conduct an NMA to evaluate the relative efficacy, in terms of OS, of fulvestrant 500 mg versus alternative therapies as treatment of postmenopausal, ER-positive ABC following failure on prior endocrine therapy.

Materials and Methods

Study Design and Data Extraction

A systematic review of the published data was conducted in November 2014 to identify relevant randomized controlled trials to compare fulvestrant 500 mg with alternative hormonal therapies for the treatment of postmenopausal women with ABC following failure on prior endocrine therapy. The following data sources were used in the literature search: databases including MEDLINE, MEDLINE In-Process, EMBASE, and the Cochrane library, and abstract databases from congresses including the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium. A prespecified search strategy was employed, using terms applicable to the population of interest (postmenopausal women with locally advanced or metastatic breast cancer and documented ER-positive status with progression or relapse after first-line hormonal therapy), outcome (OS), study design (randomized controlled trials and meta-analyses or systematic reviews), and the interventions of interest (anastrozole, diethylstilbestrol, exemestane, everolimus, fulvestrant, letrozole, medroxyprogesterone acetate, megestrol acetate, tamoxifen, toremifene, and trilostane). Studies considered eligible for inclusion in the present NMA had to have reported on ≥ 1 of the interventions of interest as monotherapy or combination therapy in the second-line setting. No language or date restrictions were applied, and each potential study identified was independently evaluated by 2 reviewers to ensure its relevance against the predetermined criteria.

Statistical Analysis

An NMA was performed to compare fulvestrant 500 mg (baseline treatment) versus comparators. OS patient-level data, based on 75% maturity, were available from CONFIRM[7]; this was the largest study analyzed with the longest study duration. Parametric distributions were fit to patient-level data from CONFIRM according to guidance provided by the National Institute for Health and Care Excellence Decision Support Unit.[14] The Weibull distribution was found to be the best-fitting distribution according to the fit of the curve and appropriateness of extrapolation beyond the trial period.

For other studies, OS Kaplan-Meier curves were digitized (Engauge Digitizer, version 4.1), and a published algorithm was used to re-create the individual-level patient data.[15] Study-level HRs were obtained by modeling pseudo individual-level patient OS data using a Weibull distribution, based on statistical and visual fit.

Data were analyzed using a fixed-effect NMA of HRs and a Bayesian approach that involved formal combination of a prior probability distribution that reflects a vague/uninformative previous belief of the possible values of the pooled relative effects, with a likelihood distribution of the pooled effect based on the observed data in the different studies to obtain a posterior distribution of the pooled relative effect.

The model parameters were estimated using Markov chain Monte Carlo techniques with WinBUGS, version 1.4.1.[16] The WinBUGS sampler was run for 50,000 iterations. These were discarded as "burn-in," and the model was run for another 50,000 iterations, upon which inferences were based. The summary treatment measure (HR) was taken to be the median of the 50,000 iterations; 95% credibility intervals (CrIs) are presented throughout, based on the 2.5 and 97.5 percentiles from the distribution of the calculated data. For each of the 50,000 iterations, each treatment was given a rank (based on the relative scale). The distribution of those ranks was presented for each treatment, and the median value was estimated. The median values were used to rank the treatments from best to worst.

Comparators of Interest and Subgroup Analyses

Three patient population scenarios were included in the analysis based on the prior treatment of patients entering each study. The overall (base-case) population included patients previously treated with AO or AI therapy. The comparators of interest were anastrozole 1 mg, letrozole 2.5 mg, fulvestrant 250 mg, exemestane 25 mg, megestrol acetate 40 mg, and everolimus 10 mg plus exemestane 25 mg. Because second-line hormonal treatment varies depending on the first-line treatment, 2 subgroups were also investigated. A post-AO (following an AO) subgroup network compared fulvestrant 500 mg with anastrozole 1 mg, letrozole 2.5 mg, fulvestrant 250 mg, and megestrol acetate 40 mg. A post-AI (following an AI) subgroup network compared fulvestrant 500 mg with fulvestrant 250 mg, exemestane 25 mg, and everolimus 10 mg plus exemestane 25 mg.

Results

Studies and Patients

From the systematic literature review, 7 relevant phase III studies that had reported OS data were identified and included in the analysis.[7,17-22] The survival data for the studies of Osborne et al[19] and Howell et al[20] were obtained from the manufacturers' clinical study reports because the OS results were not reported in the