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Progression-Free Survival with Fulvestrant 500 mg and Alternative Endocrine Therapies as Second-Line Treatment for Advanced Breast Cancer: A Network Meta-Analysis with Parametric Survival Models

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ABSTRACT

Background: Ouwens et al. and Jansen have presented methods for (network) meta-analysis of survival data by using a multidimensional treatment effect as an alternative to the synthesis of constant hazards ratios, which allow for a better fit to the data and the expected survival of competing interventions for cost-effectiveness analysis. However, results may be sensitive to the assumed underlying survival function. **Objective:** To estimate the expected progression-free survival (PFS) for fulvestrant 500 mg versus alternative hormonal therapies for postmenopausal women with advanced breast cancer who relapsed previously by means of a network meta-analysis of currently available randomized controlled trials using alternative underlying survival functions. **Methods:** Eleven randomized controlled trials were included that evaluated fulvestrant 500 mg (n = 3), fulvestrant 250 mg (n = 5), fulvestrant 250 mg loading dose (n = 3), anastrozole 1 mg (n = 3), megestrol acetate (n = 4), letrozole 2.5 mg (n = 3), letrozole 0.5 mg (n = 3), and exemestane (n = 2). PFS percentages and numbers at risk were derived from Kaplan-Meier curves and combined by means of Bayesian network meta-analysis on the basis of the difference in the shape and scale parameters of the Weibull, log-normal, and log-logistic parametric survival functions. **Results:** The log-normal distribution provided the best fit, suggesting that the proportional hazard assumption was not valid. Based on the difference in expected PFS, it was found that fulvestrant 500 mg is more efficacious than fulvestrant 250 mg, megestrol acetate, and anastrozole (−5.73 months; 95% credible interval [CrI] −10.67, −1.67). Expected PFS for fulvestrant 500 mg ranged from 10.87 (95% CrI 9.21, 13.07) to 17.02 (95% CrI 13.33, 22.02) months for the Weibull versus log-logistic distribution. **Conclusions:** Fulvestrant 500 mg is expected to be more efficacious than fulvestrant 250 mg, megestrol acetate, and anastrozole 1 mg and at least as efficacious as exemestane and letrozole 2.5 mg in terms of PFS among postmenopausal women with advanced breast cancer after failure on endocrine therapy. The findings were not sensitive to the distribution, although the expected PFS varied substantially, emphasizing the importance of performing sensitivity analyses.

Keywords: fulvestrant, metastatic breast cancer, network meta-analysis, progression-free survival.

Introduction

Health care decision making is commonly informed by randomized controlled trial (RCT) evidence of the interventions of interest for a particular disease state [1–4]. Decision makers, however, are often faced with the challenge of assessing competing interventions in the absence of an RCT comparing all interventions of interest simultaneously in a head-to-head fashion [5,6]. As an alternative, indirect treatment comparisons are advocated to provide estimates of the relative treatment effects [2,7–9]. Even when direct evidence is available for some interventions of interest, combining these with indirect comparisons in a network meta-analysis (NMA) may yield a more refined and precise estimate for the relative treatment effects [3,10].

To inform cost-effectiveness decision making, the expected survival is required for interventions that aim to increase survival. In the case of censored follow-up in RCTs, in order not to underestimate the expected survival, it is necessary to extrapolate data beyond the trial period. A recent review by Guyot and Ouwens [11] of reimbursement submissions to the National Institute for Health and Clinical Excellence identified that most time-to-event efficacy analyses were synthesized and extrapolated by using constant hazard ratios (reported or pooled). The proportional hazards assumption that underlies the evidence synthesis of survival outcomes based on reported hazard ratios is implausible if hazard functions of competing interventions cross and will result in biased expected survival estimates. Ouwens et al. [12] and Jansen [13] have presented methods for (network) meta-analysis of survival data by using a multidimensional treatment effect as an alternative to the synthesis of constant hazards ratios. With known parametric survival functions (e.g., Weibull, log-normal, or log-logistic), the survival

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functions of the interventions compared in a trial are modeled and the difference in the parameters of these functions within a trial are considered the multidimensional treatment effect, which are synthesized (and indirectly compared) across RCTs. The advantage of this approach is that models can be fitted much closer to the data and the expected survival of competing interventions for cost-effectiveness analysis (CEA) can be estimated more accurately.

Although the NMA models by Ouwens et al. can be considered a very flexible and promising approach for the evidence synthesis of survival data, it is important to evaluate the impact of the assumed survival functions (e.g., Weibull, log-normal, or log-logistic) on the expected survival estimates. This methodology is illustrated by means of an NMA of fulvestrant 500 mg (Faslodex) and alternative endocrine therapies for advanced breast cancer among postmenopausal women who have progressed on previous endocrine therapy.

Fulvestrant is an estrogen receptor (ER) antagonist with no known agonist effects. It has been approved for the treatment of postmenopausal women with ER-positive (ER+) metastatic or locally advanced breast cancer in which disease has recurred during or within 1 year of completing adjuvant antiestrogen therapy or progression on an antiestrogen (i.e., patients who have recurred or progressed after one previous endocrine therapy). The phase III Comparison of Faslodex in Recurrent Metastatic Breast Cancer (CONFIRM) trial demonstrated that fulvestrant 500 mg significantly improved progression-free survival (PFS) compared with fulvestrant 250 mg (hazard ratio 0.8; $P = 0.006$), with a nonsignificant trend toward better overall survival (OS) [14]. The efficacy benefit for fulvestrant 500 mg compared with fulvestrant 250 mg was achieved without compromising tolerability or quality of life [14]. This phase III study led to the approval of the 500-mg dose in the United States and Europe. The efficacy of the previously approved fulvestrant 250-mg regimen was evaluated in several phase II and III RCTs (FINDER1 [15], FINDER2 [16], Trial 0020 by Howell et al. [17], and Trial 0021 by Osborne et al. [18]), two of which compared fulvestrant 250 mg directly with anastrozole [17,18]. Using fulvestrant 250 mg as the common comparator, it is possible to perform an indirect comparison that allows for a comparison of fulvestrant 500 mg with anastrozole. Moreover, by extending the evidence base to include RCTs evaluating third-generation aromatase inhibitors, comparisons to anastrozole, letrozole, and exemestane are feasible by performing an NMA.

The aim of this article was to estimate the expected PFS with fulvestrant 500 mg and hormonal therapies for the management of advanced breast cancer in postmenopausal women who relapsed previously by means of an NMA based on currently available RCT evidence. In addition, we demonstrate the impact and importance of the assumed underlying survival function for the NMA.

Methods

Identification and Selection of studies

A systematic literature search was performed in January 2010 to identify published RCTs evaluating the efficacy of second-line treatment regimens for patients with postmenopausal ER+ advanced breast cancer (stage III or IV) who relapsed on prior endocrine therapy. Medline, Medline In-Process, EMBASE, and Cochrane databases as well as selected cancer-related conferences were searched by using a predefined search strategy with terms relevant to advanced breast cancer, RCTs, and the interventions of interest. In addition, study documents for fulvestrant were made available by AstraZeneca.

Two reviewers independently evaluated each identified study against the following predetermined criteria.

Population
Postmenopausal ER+ advanced breast cancer (stage III or IV) who relapsed on prior endocrine therapy.

Interventions
Fulvestrant, letrozole, anastrozole, exemestane, and megestrol acetate.

Comparisons
Placebo or one of the regimens described under interventions. Comparisons of the same intervention with different background treatments were excluded.

Outcomes
PFS or time to progression.

Study design
RCTs.

For each identified study that met the selection criteria, details were extracted on study design, study population characteristics, and interventions. The hazard ratios and associated 95% confidence intervals were extracted for PFS where reported. For all studies, except where individual patient-level data were available (CONFIRM study), the reported Kaplan-Meier curves were digitized (Engauge Digitaliser v4.1) for each treatment arm by using the progression percentages for the time points where the numbers at risk were provided [12]. When the numbers at risk were not provided, a conservative estimate of uncertainty was derived for these progression percentages by using the median duration of follow-up and death. The data set was created on the basis of extracted progression proportions, which were used to calculate the incident number of progression events for each interval and patients at risk at the beginning of that interval.

Analysis

A Bayesian NMA was performed by using the methodology proposed by Ouwens et al. [12]. With this approach, the progression of patients over time of the interventions compared in a trial is modeled with parametric survival functions and the difference in the shape and scale parameters of these functions between interventions is synthesized and indirectly compared across trials. The following parametric survival functions were used and compared: 1) Weibull, 2) log-normal, and 3) log-logistic. Additional details on these models have been reported previously by Ouwens et al. [12]. To let the shape and scale of survival distributions be positive, the log shape and log scale were modeled in the current analysis.

The first 30,000 iterations from the WinBUGS sampler were discarded as "burn-in," and the inferences were based on an additional 30,000 iterations by using two chains. The convergence of the chains was confirmed by using the Gelman-Rubin statistic. To avoid influencing the results of the analysis based on prior beliefs, noninformative prior distributions were used for the model parameters to be estimated. All models were analyzed by using Markov Chain Monte Carlo techniques with WinBUGS 1.4.1. WinBUGS codes are available from authors on request.

The deviance information criterion (DIC) was used to compare the goodness of fit of different models. DIC provides a measure of model fit that penalizes model complexity according to $DIC = \overline{D} + pD$, $pD = \overline{D} - \hat{D}$ [19]. Here $\overline{D}$ is the posterior mean residual deviance [20], pD is the effective number of parameters, and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters. The model with the lowest DIC is the model providing the "best" fit to the data.