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Fulvestrant versus anastrozole as second-line treatment of advanced breast cancer in postmenopausal women

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1. Introduction

Most patients with hormone-sensitive breast cancer currently receive tamoxifen at some stage during their treatment. However, many of these patients will eventually develop tamoxifen-resistant disease, necessitating subsequent treatment with an agent that is not cross-resistant with tamoxifen or compounds of the same class.

Newer endocrine agents that have demonstrated efficacy in the treatment of tamoxifen-resistant disease include the non-steroidal aromatase inhibitors anastrozole ('Arimidex') and letrozole, and the steroidal agent exemestane. Both anastrozole [1,2] and letrozole [3] are effective and well tolerated. Fulvestrant ('Faslodex' formerly ICI 182,780) is a new oestrogen receptor (ER) antagonist that downregulates the ER and unlike tamoxifen, is devoid of agonist effects [4]. Binding of fulvestrant to the ER induces a rapid loss of ER protein from breast cancer cells, which occurs in a dose-dependent manner as indicated by a dose-related reduction in the ER index [6]. In addition, and in contrast to tamoxifen, fulvestrant reduces tumour progesterone receptor (PgR) content [5,6]. This novel mode of action distinguishes fulvestrant from selective oestrogen receptor modulators currently in clinical use (e.g. tamoxifen, toremifene and raloxifene). This report summarises the combined analysis of two phase III clinical trials (0020 and 0021) which were prospectively designed to allow combination of results. Each trial compared a once-monthly intramuscular (i.m.) injection of fulvestrant 250 mg with a once-daily (o.d.) oral dose of the third-generation, non-steroidal, aromatase inhibitor, anastrozole 1 mg. Both were multicentre, randomised, controlled, parallel-group trials. Each trial compared the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer who had progressed on prior endocrine treatment. The results for the individual trials have previously been reported in Refs. [7,8].

2. Patients and methods

Data were combined from two trials (0020 and 0021) comparing the efficacy and tolerability of fulvestrant 250 mg given by i.m. injection once monthly with anastrozole, 1 mg o.d. orally.

2.1. Patients

All patients were postmenopausal women with locally advanced or metastatic breast cancer who progressed following adjuvant endocrine therapy (primarily with tamoxifen) or following first-line endocrine therapy for advanced disease.

2.2. Trial design

Patients were randomised to either fulvestrant 250 mg (one×5 ml (trial 0020) or two×2.5 ml (trial 0021) ($n=428$) i.m. once monthly or anastrozole 1 mg ($n=423$) orally o.d. Patients received the treatment to which they were randomised until there was objective evidence of disease progression or until withdrawal from the trial.

3. Results

3.1. Patient characteristics

The intent-to-treat (ITT) population for this combined analysis was 851 patients, 428 in the fulvestrant 250 mg group and 423 in the anastrozole 1 mg group. The majority of patients (96% in the fulvestrant group and 97% in the anastrozole group) had previously been treated with tamoxifen.

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3.2. Time to progression

The estimated median time to progression (TTP) was 1.3 months longer for patients treated with fulvestrant (5.5 months) compared with those treated with anastrozole (4.1 months), although this difference did not reach statistical significance Hazard Ratio (HR) 0.95; 95.14% Confidence Interval (CI) 0.82–1.10; $P = 0.48$). These data demonstrate a non-inferiority of fulvestrant relative to anastrozole for TTP.

3.3. Objective response rate

There was a numerical advantage for treatment with fulvestrant ($n = 82$ (19.2%)) compared with anastrozole ($n = 70$ (16.5%)). The difference in response rates of 2.75% was not statistically significant (95.14% CI −2.27–9.05%; $P = 0.3$l).

3.4. Clinical benefit (CB) rates

CB rates complete response (CR) + partial response (PR) + stable disease (SD) $\geqslant$24 weeks) for fulvestrant were 43.5% (186 patients) and for anastrozole were 40.9% (173 patients) with the analysis showing no statistically significant difference (estimated difference in clinical benefit rates 2.34%; 95% CI −4.42–9.36%; $P = 0.51$).

3.5. Tolerability

Withdrawals as a result of adverse events (AEs) (drug-related) were low: 2.8% (0.9%) in the fulvestrant group and 1.9% (1.2%) in the anastrozole group. Seven AEs were predefined for statistical analysis. The incidence of these AEs in the fulvestrant versus anastrozole treatment groups were: gastrointestinal disturbances 46.3% versus 43.7%; hot flushes 21.0% versus 20.6%; vaginitis 2.6% versus 1.9%; weight gain 0.9% versus 1.7%; thromboembolic disease 3.5% versus 4.0%; urinary tract infection 7.3% versus 4.3% and joint disorders (including arthralgia, arthrosis, arthritis) 5.4% versus 10.6%. The only AE to occur at a significantly different incidence between the two treatments was joint disorders, which was significantly less frequent in the fulvestrant group ($P = 0.0036$).

3.6. Endocrine therapy after fulvestrant

Retrospective follow-up data were available for 66 patients who demonstrated CB on fulvestrant. Of the patients who achieved CB on fulvestrant, 54 received further endocrine therapy, which in the majority of patients (46/54; 85%) was an aromatase inhibitor, either anastrozole ($n = 37$), letrozole ($n = 8$) or formestane ($n = 1$), with the remaining patients (15%) receiving megestrol acetate ($n = 8$). Subsequent endocrine therapy in this subset of patients resulted in an OR in 4/54 patients and CB in 25/54 patients.

4. Conclusions

Overall, these data demonstrate that fulvestrant, given as a 250 mg monthly i.m. injection, is at least as effective as daily oral anastrozole in the treatment of postmenopausal women with advanced breast cancer who have previously been treated with endocrine therapy. In addition, there appears to be no significant cross-resistance between fulvestrant and the different endocrine therapies examined. With its proven efficacy and good tolerability profile, fulvestrant will be a valuable new treatment option for advanced breast cancer in postmenopausal women.

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