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Original Research

Fulvestrant plus goserelin versus anastrozole plus goserelin versus goserelin alone for hormone receptor-positive, HER2-negative tamoxifen-pretreated premenopausal women with recurrent or metastatic breast cancer (KCSG BR10-04): a multicentre, open-label, three-arm, randomised phase II trial (FLAG study)☆

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Abstract ***Background:*** We investigated the efficacy and safety of fulvestrant plus goserelin (F + G) versus anastrozole plus goserelin (A + G) in comparison with goserelin (G) alone in premenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), tamoxifen-pretreated metastatic breast cancer (MBC).
Patients and methods: In this multicentre, open-label, randomised phase II study, premenopausal women aged ≥18 years with HR+, HER2−, tamoxifen-pretreated MBC were randomly assigned (1:1:1) to F + G, A + G or G alone. The primary end-point was time to progression (TTP). Secondary end-points included overall survival, overall response rate, clinical benefit rate and toxicity.
Results: Of 138 eligible patients, 44 were randomly assigned to receive F + G, 47 to A + G and 47 to G alone. The median follow-up duration was 32.2 months (interquartile range: 23.69−40.86) and the median age was 43.0 years (range 23.0−55.0). The median TTP was 16.3 months (95% confidence interval [CI] 7.5−25.1) for F + G, 14.5 months (95% CI 11.0−18.0) for A + G and 13.5 months (95% CI 10.3−16.8) for G alone. Compared with G alone, the hazard ratios were 0.608 for F + G (95% CI, 0.370−0.998; p = 0.049) and 0.982 for A + G (95% CI, 0.624−1.546; p = 0.937). In terms of visceral metastasis, a stratification factor, there were no TTP differences according to treatment arm. Grade III or IV toxicities were rarely observed. Of the common adverse events, grade I arthralgia and joint stiffness were more frequently observed in the F + G than in the A + G or G-alone groups ($p < 0.05$, respectively).
Conclusions: F + G provides a promising new option for the treatment of premenopausal women with HR+, HER2-, tamoxifen-pretreated MBC.
Trial registration: ClinicalTrials.gov number NCT01266213 and Korean Cancer Study Group (KCSG) Breast cancer protocol number BR10-04.

1. Introduction

Breast cancer remains the most common malignancy in women. Hormone receptor-positive (HR+) tumours account for about 65% of all cases in premenopausal women and about 80% of all cases in postmenopausal women [1].

The sequential use of endocrine therapies with different modes of action delays the need for chemotherapy, resulting in fewer treatment-related toxicities, greater health-related quality of life and high satisfaction with treatment [2]. The agent(s) for use in endocrine therapy can be selected according to the patient's menopausal status, type of previous endocrine treatment, disease-free interval, disease status and extent of disease, including the presence or absence of visceral metastases [3,4].

Indeed, the guidelines of the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) for advanced breast cancer recommend that endocrine therapy, rather than cytotoxic chemotherapy, be used as the standard first-line treatment for patients with HR + advanced or metastatic breast cancer (MBC) and that chemotherapy be reserved for patients who have immediate life-threatening disease or symptomatic visceral metastases or for whom the physician has concerns about endocrine resistance [5,6].

Compared with the variety of hormonal agents that are effective in treating postmenopausal women with breast cancer, a limited number of hormonal agents are effective endocrine therapy for premenopausal women with breast cancer. Tamoxifen, a selective oestrogen receptor (ER) modulator, is a well-established effective first-line hormonal agent in HR + MBC in premenopausal women [4,7,8]. In addition, medical ovarian function suppression (OFS) with gonadotropin-releasing hormone agonists (GnRH agonist) has been extensively studied in premenopausal women with advanced breast cancer since Sir George Beatson demonstrated the role of oophorectomy as a therapeutic option in 1896 [9]. A meta-analysis of four studies showed that the combination of tamoxifen and luteinising hormone-releasing hormone (LHRH) analogue prolonged progression free survival and overall survival (OS) compared with LHRH analogue alone in premenopausal advanced breast cancer [10]. Therefore, the ABC guideline recommends that ovarian suppression/ablation combined with tamoxifen is the preferred choice to tamoxifen alone [11]. However, for premenopausal patients who have been pretreated with or are