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Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer ☆

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Abstract ***Background:*** Endocrine therapy is the preferred treatment for hormone-receptor (HR) positive metastatic breast cancer. In premenopausal patients, ovarian function suppression with goserelin in combination with anastrozole yielded promising results in phase II studies. Fulvestrant, a pure antioestrogen, yields high rates of disease stabilisation in postmenopausal women. Therefore, we investigated the feasibility and safety of fulvestrant plus goserelin in premenopausal women with HR-positive metastatic breast cancer.

Methods: Premenopausal patients with metastatic breast cancer eligible for endocrine treatment received fulvestrant 250 mg and goserelin 3.6 mg every four weeks as first- to fourth-line therapy. Clinical benefit rate (CBR; response rate plus disease stabilisation $\geqslant$6 months) was defined as the primary study end-point. Time to progression (TTP) and overall survival (OS) were estimated using the Kaplan–Meier product limit method.

Findings: Twenty-six patients received treatment as scheduled. 81% were pre-treated with tamoxifen and 69% had received prior aromatase inhibitors in combination with goserelin. The majority of patients (69%) presented with visceral metastases.

Complete response was observed in a single patient, partial response in three and disease stabilisation $\geqslant$6 months in eleven patients, resulting in a CBR of 58%. Median TTP was 6 months (95% confidence interval (CI), 2.4–9.6) and OS 32 months (95% CI, 14.28–49.72), respectively.

☆ Preliminary results were presented at the 2005 ASCO Annual Meeting.

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Interpretation: Results suggest that the combination of fulvestrant and goserelin offers promising activity in premenopausal patients and further investigation is warranted.

1. Introduction

Endocrine therapy is the preferred treatment modality in hormone-receptor-positive (HR) early stage and advanced breast cancer. Sequential administration of non-cross resistant drugs prolongs the chemotherapy-free interval and yields effective disease stabilisation with limited toxicity.

Tamoxifen was the backbone of endocrine therapy for nearly three decades. In metastatic disease, response rates of up to 30% were reported.[1–3] Tamoxifen and its metabolites bind to the oestrogen receptor (ER), thereby blocking activating-function-2 (AF-2). This receptor modulation causes antagonistic as well as oestrogenic effects.[4]

A newer class of drugs, aromatase inhibitors (AIs), reduce plasma oestrogen concentrations via the inhibition of aromatase, an enzyme synthesising oestrogens from androgenic precursors produced by the adrenal glands.[5] Randomised clinical trials have demonstrated superior efficacy of third generation AIs to tamoxifen in postmenopausal women.[1,3]

Fulvestrant is a pure ER-antagonist without agonistic properties. Once bound to the receptor, ER dimerisation and nuclear translocation is inhibited,[6] resulting in accelerated receptor degradation.[6,7] Besides nuclear ER, fulvestrant blocks cytoplasmatic as well as membrane-bound receptors. It is therefore suggested that fulvestrant inhibits the ER/growth factor crosstalk responsible for ER activation in the absence of oestrogen.[7–10]

In two randomised phase III trials, fulvestrant was as active as anastrozole in postmenopausal women progressing on prior endocrine therapy.[11,12] Fulvestrant was well tolerated, and a trend towards superior efficacy was observed.

In premenopausal women, high oestrogen levels render aromatase inhibition without ovarian function suppression ineffective. Luteinising hormone releasing hormone (LHRH) agonists provide similar efficacy in terms of oestrogen level reduction as surgical oophorectomy.[13] Importantly, LHRH agonists combined with tamoxifen are superior to ovarian ablation alone.[14] Therefore, the combination of gonadotropin-releasing hormone analogues and tamoxifen is a standard of care for premenopausal women with endocrine-responsive metastatic breast cancer. Upon disease progression, selected patients may be candidates for further endocrine treatment in combination with ongoing ovarian function suppression.

In the adjuvant setting, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) established similar efficacy of goserelin plus anastrozole to goserelin plus tamoxifen.[15] In metastatic disease, goserelin plus anastrozole yielded a clinical benefit rate (CBR; complete response (CR) plus partial response (PR) plus stable disease $\geqslant 6$ months) of approximately 70%.[16]

Similarly to AIs, fulvestrant when given at the conventional dose of 250 mg, lacks activity in premenopausal women.[17] Given the high activity of fulvestrant in postmenopausal women, we initiated an observational study of fulvestrant in combination with standard ovarian function suppression in premenopausal patients with hormone receptor-positive metastatic breast cancer eligible for ongoing endocrine treatment.

2. Patients and methods

All patients were managed by a dedicated team of breast cancer specialists at an academic breast centre. The decision for endocrine treatment of metastatic disease was taken in an interdisciplinary tumour board. This study was conducted in accordance with the ethical regulations of the Medical University of Vienna and approval by the local ethics committee was obtained.

2.1. Patients

During the study period (2002–2010), thirty consecutive premenopausal patients with metastatic hormone-receptor-positive breast cancer eligible for further endocrine treatment were included.

Inclusion criteria were as follows: histologically confirmed hormone-receptor-positive metastatic breast cancer patients eligible for endocrine therapy; minimum of one prior endocrine treatment line for early stage or advanced disease; treatment with fulvestrant 250 mg plus goserelin as first to fourth-line therapy for advanced stage disease. Premenopausal status was defined by regular menstruation periods and by ensuring that luteinising hormone (LH), follicle-stimulating hormone (FSH) and oestradiol serum levels were inside the premenopausal range. In patients pretreated with goserelin and aromatase inhibitors, premenopausal status before ovarian function suppression was used as surrogate.

For baseline staging evaluations, computed tomography (CT)-scans of the chest and the abdomen, bone scan, mammography and gynaecologic examination were mandatory, with further work-up if indicated. Due to the observational design of this study, no central radiological review was performed.