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Original article

Impact of body mass index on the efficacy of endocrine therapy in patients with metastatic breast cancer - A retrospective two-center cohort study

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ABSTRACT

Bakground: The aim of this study was to investigate the impact of body mass index (BMI) on the efficacy of endocrine therapy in postmenopausal women with metastatic hormone receptor breast cancer (HR+BC) as well as to identify if the potential difference in efficacy was associated with Fulvestrant only or both aromatase inhibitors (AIs) and Fulvestrant.
Methods: A consecutive cohort of postmenopausal women with HR+metastatic breast cancer that have received endocrine therapy including Fulvestrant as a metastatic treatment strategy at the Departments of Oncology in Eskilstuna and Uppsala, Sweden, between 2008 and 2016 were identified. The primary outcome of the study was time to disease progression (TTP) during the treatment with Fulvestrant in overweight and obese women compared to patient with normal BMI.
Results: In total, 173 patients were enrolled in the study cohort, amongst these, 141 patients received both Fulvestrant and AIs and 32 received only Fulvestrant. No statistical significant association was observed between the three BMI categories and TTP, during Fulvestrant treatment ($p = 0.136$). The rates of objective response and clinical benefit due to Fulvestrant were similar among patients with normal weight, overweight and obesity, respectively.
Conclusions: No difference in treatment efficacy was seen between normal, overweight and obese women with metastatic HR+BC, when treated with Fulvestrant. Until further research with prospective studies is available, there is no evidence to support any modification in how Fulvestrant treatment is used in patients with metastatic breast cancer in regard to BMI.

1. Introduction

Obesity is not only an established risk factor for development of breast cancer but also a negative prognostic factor with higher incidence of recurrence and cancer related deaths, in both pre- and post-menopausal women [1,2]. Several mechanisms, both direct and indirect, have been suggested to explain the association between obesity and breast cancer development and subsequent mortality. The direct, also referred to as biological, mechanisms involve hyperinsulinemia, inflammation and estrogen pathways, whereas the indirect, non-biological mechanisms involve delayed presentation of disease and under-dosing of treatment [1,3]. The increased risk for developing breast cancer in obese post-menopausal women has been linked to both hormone receptor-positive (HR+) and triple-negative tumors. However, the association between obesity and poor treatment response and prognosis, in the same group of women, seems to be associated with HR+and Her2-negative tumors [2,4,5].

Estrogen synthesis in post-menopausal women occurs in peripheral, non-ovarian, mainly adipose tissues, through conversion of androgens by the enzyme aromatase [6]. Elevated levels of plasma estrogens have been measured in overweight and obese women, suggesting increased estrogen synthesis due to adiposity [7,8]. In HR+breast cancer, various endocrine therapies are used to limit the estrogen-induced tumor proliferation. Aromatase

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inhibitors (AIs), e.g. Letrozole, Anastrozole and Exemestane, reduce circulating estrogen concentrations by inhibiting aromatase, in post-menopausal women. Some studies have found a poorer response to AIs in overweight and obese women, suggesting inadequate suppression of circulating estrogen due to ineffective aromatase inhibition [7,9]. Tamoxifen, a selective estrogen receptor modulator (SERM), acts as a partial antagonist and agonist on the ER depending on the organ it acts on, resulting in the desired effects of tumor reduction and prevented bone demineralization and adverse effects such as increased risk of endometrial cancer and thromboembolic disease [6,10]. No association between Tamoxifen efficacy and BMI (Body Mass Index) has been observed in clinical studies [11]. Fulvestrant is currently the only selective estrogen receptor down-regulator (SERD) in clinical use for breast cancer treatment [12]. Fulvestrant is an ER-antagonist which binds with an affinity comparative to its actual ligand, estradiol, leading to a disrupted dimerization of ER, impaired estrogen-dependent transcription and increased ER-degradation [5]. Fulvestrant is a relatively new agent and a recent meta-analysis proved its effect to be at least equivalent, perhaps even superior to treatment with 3rd generation of AIs [12].

Some studies have shown a negative association between obesity and treatment outcome in post-menopausal women with HR+breast cancer, following endocrine treatment with AIs and Fulvestrant [13,14]. This negative association has yet to be established, and therefore no underlying mechanism has been determined. The current literature is limited, primarily due to the small sample size of existing studies and the variations in BMI-categorization. As a result, further research is required.

The aim of the study was to investigate the efficacy of endocrine therapy (AIs and Fulvestrant) in postmenopausal women with metastatic HR+breast cancer and high BMI compared to women with normal BMI. Furthermore, we sought out to identify if the potential difference in efficacy among different BMI categories was associated with Fulvestrant only or both AIs and Fulvestrant.

2. Methods

2.1. Study population

The study population consisted of a consecutive cohort of postmenopausal women with HR+metastatic breast cancer that have received endocrine therapy, including Fulvestrant, as a metastatic treatment strategy at the Departments of Oncology in Eskilstuna and Uppsala, Sweden, between 2008 and 2016. The patients were identified through electronic databases available in each center, MOSAIQ and RealQ, in Eskilstuna and Uppsala respectively.

Patients were included in the study cohort if they were postmenopausal women with metastatic HR+breast cancer that have received endocrine therapy as a metastatic treatment strategy. Endocrine therapy should include Fulvestrant at any line of treatment. Treatment with AIs was also recorded for analyses.

We excluded men with breast cancer, pre- and perimenopausal women, patients with non-HR+breast cancer, patients that have not received Fulvestrant as metastatic treatment, patients that have received endocrine therapy only in combination with other modalities e.g. chemotherapy, targeted therapies (except anti-HER2-treatment for patients with HER2-positive breast cancer), and patients that were included in cancer clinical trials.

The study was approved by the Ethical Review board in Stockholm (diary number: 2017/1104-31).

2.2. Data collection

The following data were extracted for each eligible patient: age at diagnosis, date at diagnosis, comorbidities at diagnosis, smoking habits, use of hormone replacement therapy (HRT), BMI at diagnosis; type of primary surgery, tumor histology, estrogen receptor ER-status, progesterone receptor PR-status, Ki-67, Elston-Ellis grade, Her2-status, adjuvant treatment; date of disease recurrence, sites of metastasis, performance status at start of each line of treatment, BMI at 1st line of treatment or when endocrine treatment is initiated, type of 1st, 2nd, 3rd etc. line of therapy, tumor response to each line of therapy, date of disease progression at each line of therapy, number of lines of therapy; Death, date of death, cause of death.

2.3. Outcomes and definitions

The primary outcome was the time to disease progression (TTP) during endocrine therapy with Fulvestrant in breast cancer patients in the BMI-categories overweight and obese compared to patients with normal BMI. TTP was defined as the time from treatment initiation until objective tumor progression. The BMI categories were defined as underweight (BMI $< 18.5\ kg/m^2$), normal (BMI: $18.50–24.99\ kg/m^2$), overweight (BMI: $25.00–29.99\ kg/m^2$) and obese (BMI $\geq 30.00\ kg/m^2$). However, as only 2 women (1%) were underweight, these women were considered with normal weight women in our analysis.

The secondary outcomes were: the TTP in breast cancer patients with BMI overweight and obese compared to patients with normal BMI during metastatic endocrine treatment with AIs; the clinical benefit rate (CBR) and objective response rate (ORR) due to Fulvestrant in patients BMI overweight/obese compared to normal BMI patients; the CBR and ORR due to AIs in patients BMI overweight/obese compared to normal BMI patients.

CBR was defined as the sum of complete response, partial response, or stable disease for at least 6 months due to a specific therapy. ORR was defined as the sum of complete response and partial response due to a specific cancer treatment.

2.4. Statistical analysis

Categorical variables were summarized by the number and percentage of patients in each category. Continuous variables were summarized by median and range.

For the time-to-event outcome (TTP) the potential association between variables and TTP were assessed by the Kaplan-Meier method (log rank test for statistical significance). Multivariate analysis was performed using Cox proportional hazard model, where variables with well-documented impact on TTP in HR+BC were included. The BMI (as a categorical variable) was included in the model due to the special interest on this variable on this study.

For the categorical outcomes CBR and ORR, the potential association between variables and outcome of interest were assessed by chi-squared test. Multivariate analysis was performed using logistic regression model, where variables with a well-documented impact on CBR and ORR, respectively, in HR+BC were included. The BMI (as categorical variable) was included in the models due to the special interest on this variable on this study.

All analyses were also conducted separately on patients who received endocrine therapy as an early (1st–3rd) and late ($\geq$4th) line of treatment in metastatic setting. All analyses were also performed by excluding the 2 patients that were categorized as underweight.

All analyses were stratified according to the sensitivity to endocrine therapy. Patients were categorized as sensitive to