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CLINICAL TRIAL

Impact of body mass index on the efficacy of aromatase inhibitors in patients with metastatic breast cancer

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Abstract

Purpose Higher levels of estrogen in obese patients may lead to incomplete inhibition by aromatase inhibitors (AIs). The aim of this study was to determine the impact of body mass index (BMI) on efficacy of AIs in patients with metastatic hormone receptor (HR)-positive breast cancer (BC).

Methods We performed a retrospective chart review of all female patients with metastatic HR-positive BC on an AI in first- or second-line settings and seen at our academic institution between 2001 and 2020. The primary endpoint was progression-free survival (PFS), defined as the time from start of AI to disease progression or death from any cause.

Results We identified 219 patients who had received an AI in the first- or second-line settings for metastatic HR-positive BC and with documented information on BMI. Of the 219 patients, 56% (123) had a low BMI (defined as < 27 kg/m^2) and 44% (96) had a high BMI (≥ 27 kg/m^2). The median PFS was 21.9 months (95% CI 14.5 to 28.4) in the low BMI group versus 20.2 months (95% CI 14.3 to 27.5) in the high BMI group ($p = 0.73$).

Conclusion While BMI influences efficacy of AIs in the adjuvant setting, our results suggest that in the metastatic setting, BMI may not impact the efficacy of AIs. This discrepancy could be due to other differences in disease characteristics that make complete aromatase inhibition more important in the adjuvant setting when disease burden is the lowest.

Keywords Metastatic breast cancer · Obesity · Aromatase inhibitors · Hormone positive breast cancer

Abbreviations

ABCSG	Austrian Breast and Colorectal Cancer Study Group
AI	Aromatase inhibitor
ATAC	Arimidex, Tamoxifen Alone or in Combination
BMI	Body mass index
BWEL	Breast Cancer Weight Loss
CDK	Cyclin-dependent kinase
EMR	Electronic medical record
ER	Estrogen receptor
HER-2	Human epidermal growth factor receptor 2
HR	Hormone receptor
PFS	Progression-free survival
PR	Progesterone receptor

Introduction

Aromatase inhibitors (AIs) are part of standard endocrine therapy for hormone receptor (HR)-positive breast cancer. Several studies have demonstrated the significant role of aromatase inhibitors (anastrozole, letrozole, exemestane) as adjuvant therapy in reducing the risk of recurrence in early-stage breast cancer [1–4]. Aromatase inhibitors are also widely used in the metastatic setting, where an AI in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor is considered frontline therapy for HR-positive, human epidermal growth factor receptor 2 (HER-2) negative metastatic breast cancer. This includes both premenopausal

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women where AIs are used in combination with ovarian function suppression and postmenopausal women [5–7].

Per the World Health Organization, about 40% and 15% of women worldwide are overweight and obese, respectively, and the prevalence of obesity has been increasing [8]. Obesity has been shown to be associated with poorer outcomes in breast cancer patients and there is concern that AIs may be less effective in obese patients [9]. AIs work by inhibiting the conversion of androgens to estrogen in peripheral adipose tissue. Obese postmenopausal patients have higher levels of estrogen, with one study finding 130% higher concentrations of serum estradiol levels in obese women compared with normal weight women [10]. Consequentially, higher levels of estrogen in obese patients may lead to incomplete inhibition by aromatase inhibitors, influencing their efficacy.

A retrospective analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial, which included premenopausal women with early-stage breast cancer on adjuvant anastrozole and ovarian function suppression, evaluated the impact of body mass index (BMI). The authors found that overweight patients treated with anastrozole had a 60% increased risk of disease recurrence and more than doubling in risk of death compared with normal weight patients on anastrozole. When comparing overweight patients on anastrozole with overweight patients on tamoxifen, patients on anastrozole had a 50% increase in risk of disease recurrence and threefold increase in risk of death [11]. Similar findings have been demonstrated in studies with postmenopausal women with early-stage breast cancer [12, 13].

While these findings raise concern for the efficacy of AIs in obese patients with early-stage breast cancer, there have been no recent studies evaluating this in the metastatic setting, where AIs are now part of standard first-line therapy for HR-positive breast cancer. The aim of this study was to determine the impact of BMI on efficacy of AIs in patients with metastatic HR-positive breast cancer.

Methods

Patient population

This study included all female patients (both pre- and postmenopausal) with metastatic HR-positive breast cancer on an AI (anastrozole, letrozole, or exemestane) therapy, seen in our academic institution's health system between January 1, 2001 and June 30, 2020, and with information about height and weight or BMI documented in the electronic medical record (EMR). All patients in this study were HR-positive as defined by immunohistochemistry with estimated percentages of nuclei staining of estrogen receptor (ER) and/or progesterone receptor (PR) protein $\geq 10\%$. All patients were diagnosed with only breast cancer without evidence of other malignancies. Only patients who received an AI in the first-line or second-line setting (after chemotherapy) for treatment of metastatic disease were included. Patients who had received prior hormone therapy such as tamoxifen or fulvestrant in the metastatic setting were excluded. Patients on AI treatment for less than 1 month were also excluded. This study was approved by the Institutional Review Board at the Mount Sinai Health System (STUDY-20-02162) and adhered to ethical standards set forth by the Declaration of Helsinki. Patient consent was not required per the IRB above.

Data collection

We performed a retrospective chart review to extract information on patient demographics, BMI, disease characteristics, and current and prior treatments. The primary endpoint was progression-free survival (PFS), which was defined as the time from start of treatment with AI to disease progression or death from any cause. Patients without a PFS event were censored at the last date of using AI. Follow-up occurred until March 31, 2021.

For this analysis, patients with a BMI less than 27 kg/m^2 were categorized as low BMI and patients with a BMI equal to or greater than 27 kg/m^2 were considered high BMI based on the BMI categorizations in the Breast Cancer Weight Loss (BWEL) trial [14]. The BMI of each patient was calculated as the median of all recorded BMI measurements during the AI treatment period. Drugs used in the same line with an AI were considered as partners and included anti-HER2 therapies (trastuzumab, pertuzumab, lapatinib), CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib), mTOR inhibitor (everolimus), and chemotherapies.

Statistical analysis

Continuous variables in baseline were expressed as median and range (minimum to maximum) and were compared with Wilcoxon rank sum test. Categorical variables in baseline were expressed as number and percentage (%) and compared with Fisher's exact test and Pearson's Chi-squared test. Comparisons of PFS across BMI subgroups were accomplished through Kaplan–Meier curves and log-rank tests. Cox proportional hazards regression models were used for univariate and multivariate analyses. All p values were two sided, and p values less than 0.05 were considered statistically significant.

Results

Patient population

We identified 23,244 patients with breast cancer (and no other active malignancies) in our institution's EMR based on pathology confirmed diagnosis. From this set of patients, 937 patients had ER and/or PR positive metastatic BC. Among them, 399 patients had received at least one of the AIs for treatment in the metastatic setting. Two male patients were excluded from the analysis. An additional 102 patients were excluded due to missing information on height/weight, HER2 status, and/or ER/PR staining or ER/PR staining was less than 10%. Another 76 patients were excluded as AI was used in the third or greater line setting. This resulted in a total of 219 patients who were included in the final analysis.

Baseline demographics and clinical characteristics of patients are shown in Table 1. The median age was 59 years with 45% of patients identifying as White. Thirty-two percent had HER-2 positive disease and 82% were on an AI in the first-line setting. Overall, 53% were receiving letrozole, 42% anastrozole, and 5.5% exemestane. Of the 219 patients, 56% (123) were categorized as low BMI (defined as < 27 kg/m^2), and 44% (96) as high BMI (≥ 27 kg/m^2). There were no statistically significant differences between the two BMI groups in terms of age, race/ethnicity, HER2 status, type of AI used, and type of metastatic disease (de novo versus recurrent metastatic, $p > 0.05$).

Table 1 Patient demographics and clinical characteristics

Characteristic	Total ($N=219$)	Low BMI $N=123$ (56%)[a]	High BMI $N=96$ (44%)[a]	p value[b]
Age[c]	59 (23–90)	57 (23–90)	63 (26–90)	0.089
Race/Ethnicity				0.2
White	99 (45%)	59 (48%)	40 (42%)	
Black or African American	63 (29%)	33 (27%)	30 (31%)	
Hispanic or Latino	34 (16%)	14 (11%)	20 (21%)	
Asian	12 (5.5%)	9 (7.3%)	3 (3.1%)	
Other or unknown	11 (5.0%)	8 (6.5%)	3 (3.1%)	
HER2 status				0.7
Negative	148 (68%)	82 (67%)	66 (69%)	
Positive	71 (32%)	41 (33%)	30 (31%)	
AI				0.2
Anastrozole	91 (42%)	58 (47%)	33 (34%)	
Exemestane	12 (5.5%)	6 (4.9%)	6 (6.2%)	
Letrozole	116 (53%)	59 (48%)	57 (59%)	
Line				0.4
First	179 (82%)	103 (84%)	76 (79%)	
Second	40 (18%)	20 (16%)	20 (21%)	
Drug partner				0.4
No partner (AI alone)	86 (39%)	48 (39%)	38 (40%)	
Anti-HER2	14 (6.4%)	9 (7.3%)	5 (5.2%)	
CDK4/6i	103 (47%)	53 (43%)	50 (52%)	
CDK4/6i, Anti-HER2	10 (4.6%)	8 (6.5%)	2 (2.1%)	
Chemotherapy	2 (0.9%)	2 (1.6%)	0 (0%)	
Chemotherapy, Anti-HER2	2 (0.9%)	1 (0.8%)	1 (1.0%)	
mTORi	2 (0.9%)	2 (1.6%)	0 (0%)	
Type of metastatic disease				0.8
De novo	98 (45%)	54 (44%)	44 (46%)	
Recurrent	121 (55%)	69 (56%)	52 (54%)	

[a] n (%)

[b] p values are from the Wilcoxon rank sum test for continuous variables, and from Fisher's exact test and Pearson's Chi-squared test for categorical variables (all statistical tests were two-sided)

[c] Median (Minimum–Maximum)

Progression-free survival according to BMI

One hundred thirty-six events, including 15 deaths, were included in this analysis. Overall, 54% (66) of patients in the low BMI group and 57% (55) of patients in the high BMI group had progression of disease. The median PFS was 22.1 months (95% CI 15.1 to 28.9) in the low BMI group versus 20.2 months (95% CI 14.3 to 27.5) in the high BMI group. There was no statistically significant difference in PFS detected between patients in the two BMI groups ($p = 0.73$, Fig. 1). There were 8 (6.5%) deaths in the low BMI group and 7 (7.3%) deaths in the high BMI group.

Univariate and multivariate cox regression model analyses were performed to determine the association of other variables with BMI and PFS. After adjusting for age, race/ethnicity, HER2 status, type of aromatase inhibitor, line of therapy, drug partner, and type of metastatic disease, the multivariate analysis demonstrated no impact of BMI on PFS (HR 0.91, 95% CI 0.64 to 1.30, $p = 0.6$ for BMI high group), as shown in Table 2.

We plotted the PFS of patients along with their median BMI to further explore the relationship between these variables. A LOESS (locally weighted smoothing) curve was added to this plot (Fig. 2). A slightly higher PFS was found in the BMI 27–35 region, though interpretation limited by cohort size.

Progression-free survival in the first-line AI subgroup

We performed a similar analysis in the subgroup that used AI in the first-line metastatic setting. There were no statistically significant differences in clinical characteristics between the two BMI categories (Supplementary Table 1). The median PFS was 19.3 months (95% CI 12.6 to 28.0) in the low BMI group versus 18.0 months (95% CI 14.1 to 27.5) in the high BMI group, and there was no statistically significant difference in PFS between the two BMI groups ($p = 0.44$, Supplementary Fig. 1). Multivariate analyses adjusting for other factors also demonstrated no impact of BMI on PFS in this subgroup (Supplementary Table 2).

Discussion

It is well known that obesity is a risk factor for the development of breast cancer and tends to be associated with poorer prognosis in terms of increased recurrences and shorter overall survival [15]. Studies in patients with early-stage breast cancer on adjuvant AI have demonstrated that AIs may be less efficacious in those with a higher BMI. In our study, we found that in the metastatic setting, BMI did not significantly impact the efficacy of AIs among our patient population, as suggested by the non-significant difference in PFS between those who had a low versus high BMI.

Our findings differ from prior studies in early-stage breast cancer patients on adjuvant AI which demonstrated that obese patients may have decreased efficacy of AI. In the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, postmenopausal women with early-stage breast cancer were randomized to receive anastrozole, tamoxifen, or a combination of the two. An exploratory analysis from this trial found that while overall recurrence rates were lower in patients on anastrozole compared to

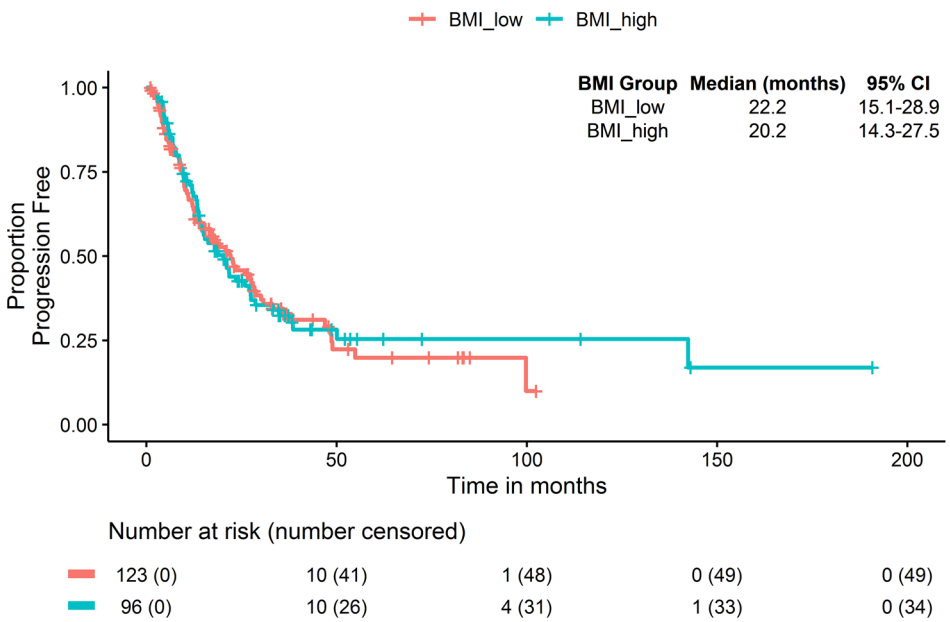

Fig. 1 Progression-free survival based on BMI. Median PFS and 95% CI for each BMI group are shown. There was no statistically significant difference in PFS between patients in the two BMI groups ($p = 0.73$; two-sided log-rank test)

Table 2 Multivariate analysis of factors affecting PFS

Characteristic	Number $N=219$[a]	Multivariate analysis		
		HR	95% CI	*p* value
Age[b]	59 (23–90)	1.01	0.99, 1.02	0.4
BMI group				
BMI low (< 27)	123 (56%)	–	–	
BMI high (≥ 27)	96 (44%)	0.91	0.64, 1.30	0.6
Race/Ethnicity				
White	99 (45%)	–	–	
Black or African American	63 (29%)	1.40	0.92, 2.12	0.12
Hispanic or Latino	34 (16%)	1.09	0.65, 1.85	0.7
Asian	12 (5.5%)	1.32	0.61, 2.83	0.5
Other or unknown	11 (5.0%)	1.30	0.54, 3.11	0.6
HER2 status				
Negative	148 (68%)	–	–	
Positive	71 (32%)	1.16	0.75, 1.79	0.5
AI				
Anastrozole	91 (42%)	–	–	
Exemestane	12 (5.5%)	1.00	0.46, 2.16	> 0.9
Letrozole	116 (53%)	0.70	0.47, 1.04	0.079
Line				
First	179 (82%)	–	–	
Second	40 (18%)	0.75	0.45, 1.25	0.3
Drug partner				
–	86 (39%)	–	–	
Anti-HER2	14 (6.4%)	0.76	0.35, 1.64	0.5
CDK4/6i	103 (47%)	0.85	0.58, 1.26	0.4
CDK4/6i, Anti-HER2	10 (4.6%)	0.22	0.05, 0.95	0.043
Chemotherapy	2 (0.9%)	0.66	0.09, 5.13	0.7
Chemotherapy, Anti-HER2	2 (0.9%)	1.05	0.14, 8.07	> 0.9
mTORi	2 (0.9%)	0.88	0.11, 6.94	> 0.9
Type of metastatic disease				
De novo	98 (45%)	–	–	
Recurrent	121 (55%)	1.09	0.76, 1.55	0.6

HR Hazard Ratio, *CI* confidence interval

[a]*n* (%)

[b]Median (Minimum–Maximum)

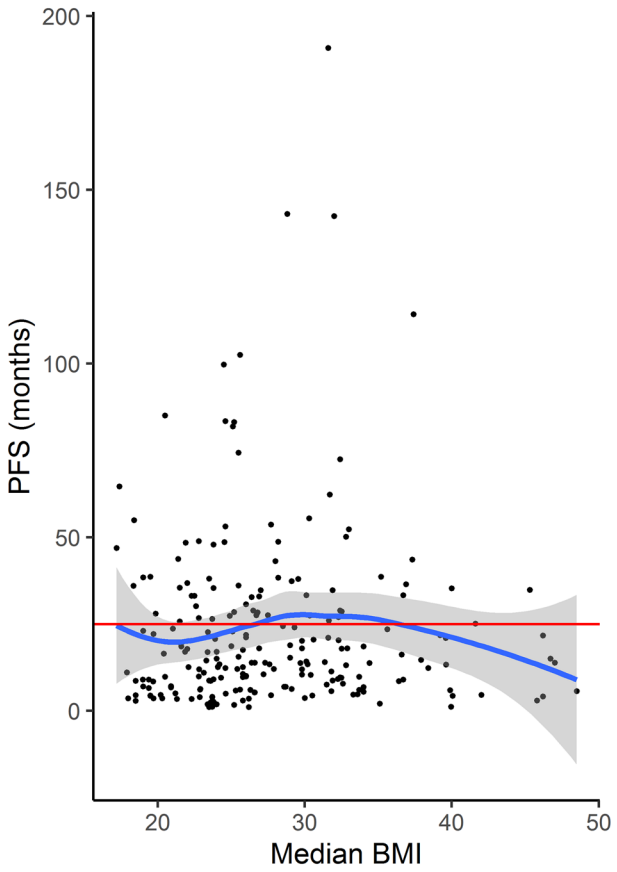

Fig. 2 Scatter plot of PFS along with median BMI. PFS was plotted against median BMI for each patient. The blue line is a local polynomial regression fitting. The red line corresponds to PFS of 25 months. A peak was found in the BMI 27–35 region

tamoxifen, in women with BMI > 30, there was no significant difference in disease recurrence between anastrozole and tamoxifen [12]. Other analyses from the ABCSG-6a trial on postmenopausal women with early-stage HR-positive breast cancer demonstrated that while normal weight patients had decreased risk of cancer recurrence and death with additional three years of adjuvant anastrozole, no benefits were seen in overweight and obese patients [13].

While these studies have shown the decreased efficacy of adjuvant AIs in obese patients, our results suggest that in the metastatic setting, BMI may not significantly impact the efficacy of AIs. This discrepancy may reflect other differences in disease characteristics between the metastatic and adjuvant setting that make complete aromatase inhibition more important in the adjuvant setting when disease burden is the lowest. A recent study in 5099 patients with HER-2 positive breast cancer found that in patients with early-stage breast cancer, higher BMI was associated with worse overall survival while in patients with advanced breast cancer, higher BMI was associated with improved overall survival [16]. This obesity paradox may account for some of the differences in the impact of BMI on AI efficacy between the early and metastatic settings.

Our findings are comparable to those of early retrospective studies which indicated that BMI did not influence outcomes in patients with metastatic breast cancer on AI. A retrospective study by Michaud et al. (2002) of 1021 postmenopausal women with metastatic breast cancer on anastrozole did not find any differences in disease progression or duration of clinical benefit based on BMI < 30 versus BMI > 30 [17]. Similarly, Schmid et al. (2000) found that in postmenopausal women with breast cancer and soft tissue metastases, women with a BMI < 30 had a similar response rate to letrozole compared to women with a BMI > 30 [18].

In another retrospective study of 173 post-menopausal women with metastatic breast cancer on fulvestrant with or without AI, there was no difference in time to disease progression based on BMI [19].

Possible limitations of our study include our small cohort size, which could be contributing to the observed discrepancy. In addition, only about 39% of patients in our study received an AI alone and more than 47% received an AI in combination with a CDK 4/6 inhibitor. It is possible that the high efficacy of CDK 4/6 inhibitors may be attenuating the effect of BMI on AIs. Other limitations include the important role of metabolic factors other than BMI that were not measured in our study. Prior studies have demonstrated that high blood pressure, elevated triglyceride levels and hyperglycemia among other factors involved in metabolic syndrome are associated with poorer outcomes in patients with early-stage and metastatic breast cancer [20, 21]. Future studies should evaluate the role of these factors in addition to BMI on AI efficacy.

Taken together, the data from these studies and our current study suggest that unlike the adjuvant setting, in the metastatic setting, there are several other patient and disease factors involved and as such BMI does not appear to have as strong an influence on outcomes in breast cancer patients on AIs. Additional multi-variate analyses from our study indicated that the impact of BMI on AI efficacy was not influenced by age, HER-2 receptor status, type of aromatase inhibitor, line of therapy, drug partner, and type of metastatic disease. There may be additional tumor and patient characteristics contributing to the differences between the metastatic and adjuvant settings.

In the last decade, AIs have been increasingly used since being approved in combination with a CDK 4/6 inhibitor for first-line treatment of metastatic HR-positive breast cancer [5–7]. The prevalence of obesity has also increased during this time [8]. Since these changes, there have not been any recent studies evaluating the relationship between obesity and AI efficacy in patients with metastatic breast cancer. Our current study results suggest that BMI may not influence AI efficacy in patients with metastatic breast cancer. Considering the increased prevalence of obesity and use of AIs in HR-positive metastatic breast cancer, these findings are highly relevant to clinical practice. Larger prospective studies are needed to confirm the findings of our retrospective analysis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06504-0.

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Data availability De-identified data will be stored until completion and publication of study. It is available from the corresponding author on reasonable request.

Code availability R (version 4.0.3) was used for analysis. Custom code is available upon reasonable request.

Declarations

Conflict of interest R.P., B.S.Z., and A.T. report no conflicts of interest. Z.L., M.Y.F., J.D.W., X.Z., and A.R. report being employees of Sema4. K.A., S.N., and R.C. report being employees of Sema4 and holding company stock/stock options. E.S. reports being Chief Executive Officer and board member for Sema4 and on the scientific advisory board for Berg Pharma. W.K.O. reports serving as a consultant to Astellas, Astra-Zeneca, Bayer, Janssen, Pfizer and Sanofi. He also serves as Chief Medical Science Officer for Sema4.

Ethical approval This study was approved by the Institutional Review Board at the Mount Sinai Health System (STUDY-20-02162).

Consent to participate Waiver for consent for this retrospective study was obtained from the Institutional Review Board at the Mount Sinai Health System.

Consent for publication All authors have reviewed this version of the manuscript and provided consent for publication.

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