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Efficacy of adjuvant aromatase inhibitor in hormone receptor-positive postmenopausal breast cancer patients according to the body mass index

MAN Sendur*[,1], S Aksoy[2], N Zengin[1] and K Altundag[2]

[1]Department of Medical Oncology, Ankara Numune Education and Research Hospital, Sihhiye, Ankara 06100, Turkey; [2]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

BACKGROUND: Increased adiposity may trigger signalling pathways that induce aromatase expression. As aromatase inhibitors exert their effects by blocking the aromatase enzyme, higher body mass index (BMI) can reduce the effect of aromatase inhibitors. Thus, we aimed to investigate retrospectively the effect of BMI on the efficacy of aromatase inhibitors in hormone receptor-positive postmenopausal patients with breast cancer.

METHODS: Newly diagnosed hormone receptor-positive breast cancer patients who were postmenopausal and non-metastatic were enrolled to the study. Patients with BMI ranging between 18.5 and 24.9 $kg\,m^{-2}$ were considered as normal weight patients (Arm A, $n=102$), and patients with a BMI ranging $\geqslant 25\,kg\,m^{-2}$ were grouped as overweight and obese patients (Arm B, $n=399$).

RESULTS: In both normal weight and overweight patients, the baseline clinico-pathologic properties and the treatment history with radiotherapy and chemotherapy were similar, and with no statistically significant difference. In normal weight patients disease-free survival (DFS) rate was 93.7% and 77.6%, whereas in overweight and obese patients DFS rate was 96.8% and 85.5% in the first and third years, respectively, ($P=0.08$). Three year survival rate in Arm A patients was 98.3%, whereas in Arm B was 98.0% ($P=0.57$). When anastrozole was compared with letrozole in the subgroup analysis no difference with regard to DFS and overall survival was detected.

CONCLUSION: These results, contradictory to the prior results, show that BMI has no worse effect on outcomes of aromatase inhibitors in postmenopausal hormone receptor-positive breast cancer patients. In the subgroup analysis, letrozole and anastrozole had similar survival outcomes.

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Aromatase inhibitors have been widely used in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer. In the adjuvant hormonal treatment of postmenopausal breast cancer patients, most of the trials have showed the superiority of aromatase inhibitors over tamoxifen (Baum *et al*, 2002, 2003; Goss *et al*, 2005; Howell, 2005; Thürlimann *et al*, 2005; Coates *et al*, 2007; Coombes *et al*, 2007; Kaufmann *et al*, 2007; Forbes *et al*, 2008; Mouridsen *et al*, 2009). Owing to the better progression-free survival rate and lower recurrences with aromatase inhibitors compared with tamoxifen in early breast cancer, aromatase inhibitors have been accepted as first line treatment in the adjuvant treatment of hormone receptor-positive postmenopausal breast cancer (Burstein *et al*, 2010).

Obesity is an independent risk factor for the development of breast cancer especially in postmenopausal women and the risk of recurrence in obese patients is significantly increased compared with non-obese patients (Loi *et al*, 2005; Reeves *et al*, 2007). Overweight or obese postmenopausal women exhibit a three-fold increased risk for developing breast cancer compared with normal weight postmenopausal women (Morimoto *et al*, 2002; Gunter *et al*, 2009). These associations have been attributed to the abnormal high expression of the enzyme aromatase in the breast that leads increased local oestrogen production, hence a predisposition to developing breast cancer (Bulun *et al*, 2012). Aromatase inhibitors act by inhibiting the conversion of androgens to estrogens, in the peripheral tissue. In postmenopausal women increased body weight is correlated with increasing adiposity. Increased adiposity may trigger signalling pathways that induce aromatase expression. On these grounds, we hypothesised that as aromatase inhibitors exert their effects by blocking the aromatase enzyme, higher body mass index (BMI) may reduce the effect of aromatase inhibitors.

In the retrospective analyses of a phase III BIG (The Breast International Group) 02-98 trial, obesity remained an independent prognostic factor for overall survival (OS) and disease-free survival (DFS) in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing regimen (de Azambuja *et al*, 2010). In another trial, retrospective subgroup analyses of 4636 patients in the Breast Cancer Care Under Evidence-based

*Correspondence: Dr MAN Şendur; E-mail: masendur@yahoo.com.tr
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guidelines project has showed that BMI had no influence on recurrence-free survival (RFS) in hormone receptor-negative patients, whereas a significantly shorter RFS was reported in postmenopausal obese patients when compared with non-obese patients (Wolters *et al*, 2012). The Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) has showed a 60% increase of disease recurrence and three-fold increase of death in overweight and obese patients compared with normal weight patients, who were treated with anastrozole plus goserelin in premenopausal breast cancer patients (Pfeiler *et al*, 2011). In the ABCSG-12 trial, DFS was similar between anastrozole and tamoxifen-treated normal weight patients but there was a 49% increased risk of recurrence in the anastrozole group compared with tamoxifen in overweight and obese patients (Pfeiler *et al*, 2011). In ATAC (arimidex, tamoxifen, alone or combination) trial women who had a BMI $\geqslant 35\,kg\,m^{-2}$ were found to have an increased risk of recurrence when compared with women with a BMI $<23\,kg\,m^{-2}$ (Sestak *et al*, 2010). In the ATAC trial, the risk of recurrence in obese women was observed only in patients treated with anastrozole, but not in those treated with tamoxifen (Sestak *et al*, 2010). In a recent trial, the ALIQUOT (Anastrozole *vs* Letrozole, an Investigation of Quality Of Life and Tolerability) study, has showed that baseline plasma estradiol and estrone sulphate levels were significantly correlated with BMI. In this study, baseline estradiol values were nearly three times higher in women with BMI $>35\,kg\,m^{-2}$ compared with BMI $<25\,kg\,m^{-2}$ (Folkerd *et al*, 2012). Anastrozole *vs* Letrozole, an Investigation of Quality Of Life and Tolerability (ALIQUOT) study, also revealed that letrozole leads to more complete inhibition of whole body aromatase compared with anastrozole, and that letrozole induced significantly greater suppression of both estradiol and estrone compared with anastrozole (Geisler *et al*, 2002; Folkerd *et al*, 2012).

Here, in this study we aimed to investigate retrospectively the effect of BMI on the efficacy of aromatase inhibitors in hormone receptor-positive postmenopausal patients with breast cancer.

PATIENTS AND METHODS

Newly diagnosed breast cancer patients from 2001 to 2012 in our clinic were retrospectively analysed. Between 2001 and 2012 years, 2218 patients with breast cancer were admitted to our clinic. Breast cancer patients who were postmenopausal at the time of diagnosis were enrolled to the study. Of the 988 postmenopausal breast cancer patients, triple-negative and hormone receptor-negative HER2 overexpression patients ($n=155$ patients), patients with metastatic disease at the time of the diagnosis ($n=188$ patients) and patients with unavailable BMI values ($n=144$ patients) were excluded from the analysis. In conclusion, a total of 501 hormone receptor-positive postmenopausal breast cancer patients were analysed (Figure 1). Patients with BMI ranging between 18.5 and $24.9\,kg\,m^{-2}$ were considered as normal weight patients (Arm A, $n=102$), whereas patients with a BMI ranging $\geqslant 25\,kg\,m^{-2}$ were grouped as overweight and obese patients (Arm B, $n=399$). Demographic and medical data including age, menopausal status, weight, height, type of breast surgery, breast cancer treatment history, radiotherapy history, hormonal treatment history, and comorbid diseases were collected from the medical charts. BMI was calculated with baseline height and weight. Tumours were graded according to the modified Bloom–Richardson scoring system and staged according to the TNM criteria. The data on ER, PR, and HER2/neu were obtained through standard clinical testing, using immunohistochemistry for ER and PR, and the HerceptTest for HER2/neu. For ER and PR, receptor positivity was based on $<5\%$ of cells testing positive. The patients were categorised as triple-negative if they were negative for ER, PR, and Her2/neu.

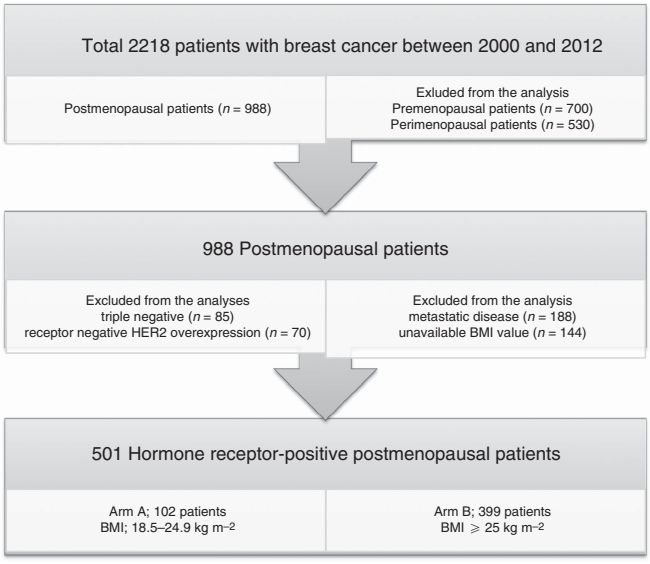

Figure 1 CONSORT diagram of the study.

Statistical analysis

Statistical analyses was performed by using SPSS for Windows version 18.0.(SPSS, Chicago, IL, USA) Baseline characteristics of normal weight patients were compared with overweight and obese patients by χ^2-tests (for categorical variables) or two sample *t*-tests (for continuous variables). Tumours with missing values were omitted from the analyses. The data were retrospectively analysed for DFS and OS according to the BMI. Kaplan–Meier survival analysis was carried out for DFS and OS. The log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided *P*-values of <0.05 were considered statistically significant.

RESULTS

A total of 501 postmenopausal hormone receptor-positive breast cancer patients were included in this study. Patients with baseline BMI ranging between 18.5 and $24.9\,kg\,m^{-2}$ were considered as normal weight patients (Arm A, $n=102$), whereas patients with a BMI ranging $\geqslant 25\,kg\,m^{-2}$ were grouped as overweight and obese patients (Arm B, $n=399$). The median follow-up time for this analysis was 25.1 months. The mean age was 58.0 ± 10.6 and 59.1 ± 8.1 in Arm A and Arm B, respectively ($P=0.37$). The mean BMI was $22.7\pm0.2\,kg\,m^{-2}$ and $31.0\pm0.2\,kg\,m^{-2}$ of Arm A and Arm B, respectively ($P=<0.001$). Baseline clinical characteristics of the participants are described in Table 1. In both arms, histology of the primary tumour and type of surgery was similar. Also in both arms the incidence of lymphovascular invasion, perineural invasion, extracapsular extension, HER2 positivity, and histological grade were similar. There were no apparent differences in baseline nodal status ($P=0.89$), tumour size ($P=0.36$) and tumour stage ($P=0.78$) between the two treatment arms. For ER and PR status; 401 (80.3%) patients have both ER and PR positivity, 438 (87.4%) patients have ER positivity, 464 (92.9%) patients have PR positivity. The distribution of the receptor pattern in both the group was not statistically significant ($P=0.13$).

Baseline treatment modalities of the participants in both the groups are described in Table 2. In both the groups the treatment history with radiotherapy ($P=0.44$) and chemotherapy ($P=0.85$) was similar, and not statistically significant. As a hormonal

Table 1 Baseline clinical characteristics by BMI of hormone receptor-positive postmenopausal breast cancer patients

	BMI				
	Arm A BMI < 25 kg m^{-2}		Arm B BMI ⩾ 25 kg m^{-2}		
Characteristic	***n***	**%**	***n***	**%**	***P*-value**
Total	102	100	399	100	
Histology of primary tumour					
IDC	66	64.7	264	66.2	
ILC	8	7.8	44	11.0	
IDC + ILC	12	11.8	33	8.3	0.28
Others	16	15.7	58	14.5	
Type of surgery					
BCS	53	52.0	222	55.6	0.78
MRM	49	48.0	177	44.4	
LVI					
Positive	28	59.6	116	63.7	0.61
Negative	19	40.4	66	36.3	
PNI					
Positive	7	14.6	22	12.1	0.62
Negative	41	85.4	160	87.9	
ECE					
Positive	21	43.7	74	40.7	0.74
Negative	27	56.3	108	59.3	
HER2					
Positive	16	16.2	63	16.2	1.0
Negative	83	83.8	326	83.8	
Tumour histological grade					
I	16	16.8	55	15.1	0.91
II	50	52.6	197	54.0	
III	29	30.6	113	31.9	
Tumour stage at diagnosis					
T1	30	29.4	131	32.8	0.36
T2	44	43.1	201	50.4	
T3	22	21.6	57	14.3	
T4	6	5.9	10	2.5	
Lymph nodal status					
N0	35	34.3	160	40.1	0.89
N1	35	34.3	123	30.8	
N2	18	17.7	63	15.8	
N3	14	13.7	43	13.3	
TNM					
Stage I	26	25.5	87	21.8	0.78
Stage IIA	21	20.6	109	27.3	
Stage IIB	21	20.6	63	15.8	
Stage IIIA	16	15.7	60	15.0	
Stage IIIB	8	7.8	35	8.8	
Stage IIIC	10	9.8	45	11.3	

Abbreviations: BCS = breast-conseving surgery; BMI = body mass index; ECE = extracapsular extension; HER = hercept test for Her2/Neu; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LVI = lymphovascular invasion; MRM = modified radical mastectomy; PNI = perineural invasion; TNM = tumour-node-metastases.

treatment in Arm A, 39/102 (38.2%) of patients were treated with anastrozole, whereas 63/102 (61.8%) of patients were treated with letrozole. In Arm B, 174/399 (43.6%) of patients were treated with anastrozole, whereas 225/399 (56.4%) of patients were treated with letrozole. In both the groups the distribution of hormonal treatment options was similar, and the difference was not statistically significant ($P = 0.37$).

Table 2 Patients treatment modalities by BMI

	BMI				
	Arm A BMI < 25 kg m^{-2}		Arm B BMI ⩾ 25 kg m^{-2}		
Characteristic	***n***	**%**	***n***	**%**	***P*-value**
Total	102	100	399	100	
Chemotherapy					
No	6	5.9	24	6.0	0.85
Adjuvant	90	88.2	337	84.5	
Neoadjuvant	6	5.9	38	9.5	
Chemotherapetic agents					
Antracycline	38	39.6	157	41.9	0.64
Taxanes	30	31.2	134	35.7	
Trastuzumab	16	16.7	54	14.4	
Others	12	12.5	30	8.0	
Radiotherapy					
No	34	33.3	119	29.8	0.44
Yes	68	66.7	280	70.2	
Hormonal treatment					
Anastrozole	39	38.2	174	43.6	0.37
Letrozole	63	61.8	225	56.4	

Abbreviation: BMI = body mass index.

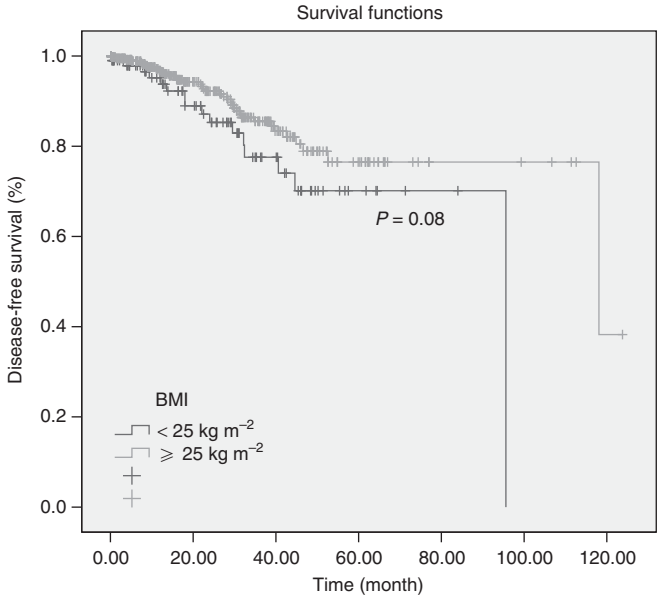

Figure 2 Analysis of disease-free survival according to the BMI.

In survival analysis the estimated median DFS was 96 months in Arm A, whereas 118 months in Arm B ($P = 0.08$) (Figure 2). In patients with normal weight patients DFS rate was 93.7% and 77.6% whereas in overweight and obese patients DFS rate was 96.8% and 85.5% in the first and third years, respectively. Median OS could not be obtained because of low number of events in both the groups (Figure 3). Three year survival rate in Arm A users was 98.3%, whereas in Arm B was 98.0% ($P = 0.57$). When anastrozole was compared with letrozole in the subgroup analysis, no difference with regard to DFS and OS was detected. Three year survival rate was 99.5% in patients treated with anastrozole, 97.0%

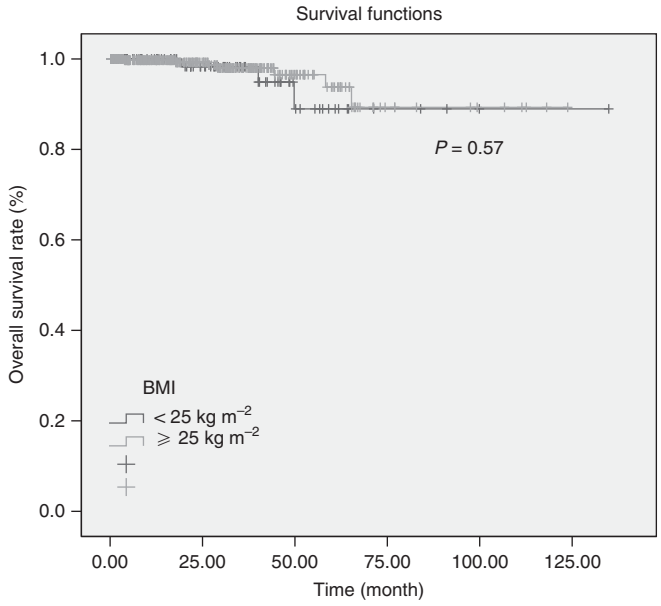

Figure 3 Analysis of OS according to the BMI.

when patients treated with letrozole in both the normal weight patients group and in overweight and obese patients group ($P = 0.49$).

DISCUSSION

Obesity is a risk factor for breast cancer in postmenopausal women and weight gain after diagnosis of breast cancer is associated with decreased survival and less favourable clinical characteristics such as greater tumour burden, higher grade, and poorer prognosis (Loi *et al*, 2005; Ellsworth *et al*, 2011). Jiralerspong *et al* (2011) reported that in early-stage breast cancer patients, higher BMI was associated with postmenopausal status and survival outcomes were significantly worse in the obese group compared with normal weight patients. This study also has showed that BMI was associated with worse outcomes especially in the chemo-treated group. In another recent Breast Cancer Pooling Project study, Kwan *et al* (2011) reported that pre-diagnosis under-weight and obese patients had a statistically significant increased overall death compared with the normal weight patients. Also, most of the obese patients have been shown to be more likely to receive lower doses chemotherapy than their actual BMI, when compared with normal BMI patients, thus the dose reduction of the doses of chemotherapy may have negative impact on outcomes (Colleoni *et al*, 2005).

Obesity has been associated with abnormally high expression of the enzyme aromatase in the breast, increased local oestrogen production and predisposition to the cancer and recurrence (Bulun *et al*, 2012). In postmenopausal women, fat tissue is the major source of estrogens, thus the higher aromatase enzyme levels in obese patients can increase the oestrogen levels. On these grounds, expression of aromatase enzyme increased with high BMI, may influence the effect of aromatase inhibitors (Rose *et al*, 2004). In ATAC trial, women who had a BMI $\geqslant 35\,kg\,m^{-2}$ were found to have an increased risk of recurrence as compared with women with a BMI $< 23\,kg\,m^{-2}$ and the risk of recurrence in obese women was seen only in patients treated with anastrozole, not in tamoxifen-treated obese patients (Sestak *et al*, 2010). In ABCSG-12 trial, DFS was similar between anastrozole and the tamoxifen groups in normal weight patients, but there was a 49% increased risk of recurrence in the anastrozole-treated group when compared with the tamoxifen group in premenopausal overweight and obese hormone receptor-positive breast cancer patients (Pfeiler *et al*, 2011).

In our study, we have showed that the 1 and 3 year DFS rate and 3 year OS rate were similar in normal weight patients and overweight and obese patients. In the subgroup analysis both letrozole and anastrozole had similar DFS and OS rates in normal weight patients and overweight and obese patients. Previous studies have demonstrated that letrozole leads to greater degree of inhibition of aromatase enzyme when compared with anastrozole in postmenopausal breast cancer patients (Geisler *et al*, 2002). In a recent trial, the ALIQUOT study has showed that baseline plasma estradiol and estrone sulphate levels were significantly correlated with BMI and letrozole induced significantly greater suppression of both estradiol and estrone sulphate compared with anastrozole (Folkerd *et al*, 2012). In this study, Folkerd *et al* (2012) demonstrated that baseline estradiol values were nearly three times higher in women with BMI $> 35\,kg\,m^{-2}$ compared with BMI $< 25\,kg\,m^{-2}$. The clinical benefit of this complete inhibition of letrozole compared with anastrozole is still unclear, because there is no randomized phase III clinical trial that directly compares the efficacy of both letrozole and anastrozole. In postmenopausal patients, a randomized phase II trial compared the efficacy of aromatase inhibitors in the neoadjuvant setting. This study has showed that in the neoadjuvant setting both letrozole and anastrozole have similar rates of clinical response (Ellis *et al*, 2011).

Our study showed the equally effective of aromotase inhibitors in overweight and obese patients compared with normal weight patients. To our knowledge, this is the first study that compared the efficacy of both letrozole and anastrozole in the postmenopausal hormone receptor-positive early breast cancer according to the BMI. The diversity of our study, only postmenopausal hormone receptor-positive breast cancer patients analysed in our study compared ABCSG-12, and only aromatase inhibitors analysed in our study compared with ATAC and ABCSG-12 trial. Our study includes some limitations, which are inherent to its retrospective nature. Lower doses of chemotherapeutic agents may have been administered to overweight and obese patients. Retrospective analyses and observational studies suggest that dose limitations in obese patients may compromise DFS and OS rates (Abdah-Bortnyak *et al*, 2003; Griggs *et al*, 2012). The short duration of follow-up is another limitation of our study. Another critique limitation of our study, we have only the data of baseline BMI values. Our baseline data does not reflect the possibility that some previously 'normal' BMI women became overweight or obese during the follow-up period or vice versa.

In conclusion, our retrospective analysis has demonstrated that BMI has no negative impact on outcomes in postmenopausal hormone receptor-positive breast cancer patients. In the subgroup analysis, letrozole and anastrozole had similar survival outcomes. Further prospective studies are needed to illuminate the role of BMI.

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