The influence of obesity on the recurrence of cancer in HER-2 positive breast cancer patients related to adjuvant trastuzumab treatment

Obezitenin HER-2 pozitif meme kanseri hastalarında adjuvan trastuzumab tedavisi ile ilişkili olarak tümör nüksüne etkisi

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Abstract

Purpose: Trastuzumab, a humanized monoclonal antibody, was shown to prolong survival in female HER-2 positive early stage breast cancer patients. We examined whether obesity had an influence on the recurrences of HER-2 positive patients, as related to adjuvant trastuzumab treatment, retrospectively.

Materials and methods: Among HER-2 positive 170 patients, 129 had accessible data, and with 114, recorded weight / height measurements were statistically analyzed.

Results: Of these, the body mass index (BMI) was <30 kg/m^2 in 68 (60%), and ≥30 kg/m^2 in 46 (40%). Recurrence-free survival (RFS) was 8.8 ± 6.5 and 78.09 ± 12.43 months in the groups with low and high BMI, respectively (p=0.32). Recurrences were found in 7 of 95 (7.4%) receiving Trastuzumab and 13 of 34 patients (38.2%) not receiving. The difference was significant (p<0.001). We detected that 53 patients have a carcinoma insitu on the pathological report (32 patients were BMI<30 kg/m^2 group and 21 patients were BMI ≥ 30 kg/m^2 group). Cox regression analysis showed that only presence of carcinoma in situ was significant for PFS, in the population of the study, HR 0.44 (95% CI 1.05-34.28, p=0.044). There was a significant relationship favoring trastuzumab treatment between size of tumor (p=0.04) and hormone receptor positivity with RFS (p =0.002). Moreover, in the hormone receptor negative group, the risk of recurrence was 7.6 folds in the absence of trastuzumab treatment. Median follow-up was 24 months (range 3-257) and recurrence was found in 20 patients (15.5 %). Five patients died during follow-up. Presence of carcinoma-in-situ and use of Trastuzumab had influenced RFS in the population of the study. Rate of hormone receptor negativity was higher and RFS was longer in obese patients than non-obese patients; however, the difference was not significant (p =0.659).

Conclusion: Trastuzumab is effective in breast cancer patients to prevent the recurrence, particularly in hormone receptor negative patients.

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Key words: Adjuvant therapy, HER-2, breast cancer, trastuzumab, obesity

Özet

Amaç: Humanize monoklonal bir antikor olan trastuzumabın, HER-2 pozitif erken evre meme kanseri tanılı kadınlarda sağkalımı uzattığı gösterilmiştir. Retrospektif olarak HER-2 pozitif meme kanserinde trastuzumabın etkisinin obezite ile değişip değişmediğini araştırdık.

Gereç ve yöntem: HER-2 pozitif 170 hastanın 129'unun verilerine ulaşılabildi ve 114 hastanın istatistik analiz için kayıtlardan bulunabilen boy/kilo ölçümleri elde edilebildi. Bu hastalardan vücut kitle indeksi (VKİ) <30 kg/m^2 olan grupta 68 (60%) hasta ve ≥30 kg/m^2 olan grupta 46 (40%) hasta mevcuttu.

Bulgular: Progresyonsuz sağkalım VKİ<30 kg/m^2 olan grupta 8.8 ± 6.5 ay iken, VKİ≥30 kg/m^2 grupta 78.09 ± 12.43 ay olarak hesaplandı ve aradaki fark istatistiksel olarak anlamlı değildi (p=0.32). Trastuzumab verilen 95 hastanın 7'sinde (%7.4) progresyon saptanırken, verilmeyen grupta 34 hastanın 13'ünde (%38.2) progresyon mevcuttu. Aradaki fark istatistiksel olarak anlamlıydı (p<0.001). Karsinoma insitu saptanan 53 hastanın 32'si VKİ<30 kg/m^2 olan grupta, 21'I de VKİ ≥ 30 kg/m^2 olan grupta idi. Cox regresyon analizinde ise sadece karsinoma insitu varlığı ile progresyonsuz sağkalım arasında anlamlı ilişki mevcuttu. [HR 0.44 (95% CI 1.05-34.28, p=0.044)]. Trastuzumab tedavisi ile tümör çapı (p=0.04), hormone reseptör pozitiflik durumu ile progresyonsuz sağkalım arasında anlamlı ilişki saptandı (p=0.002). Ayrıca, hormone reseptör negatif olan hastalarda Trastuzumab almadıkları takdirde, nüks riskinin 7.6 kat arttığı saptandı. Takip süresi median 24 ay (sınırlar 3-257 ay) olup, 20 hastada (%15.5) nüks saptandı. Takipte 5 hasta ex oldu. Tüm hasta grubunda Trastuzumab kullanımı ve karsinoma insitu varlığı progresyonsuz sağkalımla ilişkili idi. Hormon reseptör negatifliği ve progresyonsuz sağkalım obez hastalarda daha uzundu ama aradaki fark anlamlı değildi (p =0.659).

Sonuç: Trastuzumab, meme kanserinde özellikle hormon reseptör negatif olan hastalarda progresyonu önlemede etkili bulundu.

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Anahtar sözcükler: Adjuvan tedavi, HER-2, meme kanseri, trastuzumab, obezite

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Introduction

Breast cancer is the most common cancer in women. Early detection, improved chemotherapeutic regimens, and targeted treatments like trastuzumab, have resulted in substantial improvements in the survival of patients with breast cancer.

It was reported that positive association has been detected between obesity and breast cancer in postmenopausal women [1,2]. Body mass index (BMI) is widely used to define obesity clinically. Obesity is defined as the calculated BMI value (weight [kg]/body surface area [m^2]) ≥30 kg/m^2 [3]. Obesity is directly related to breast cancer in postmenopausal women, while it was reported in several studies that obesity is inversely related with breast cancer in premenopausal patients [4-8]. In a study conducted in Norway and Sweden, this finding was validated, excluding breast cancer patients with familial history [6]. It has been suggested that dual effect of obesity related to menopausal status. Authors advocated that this condition could be valid only for developed countries and young obese patients [7,8]. Obesity has a worse outcome on prognosis of women diagnosed to have early stage breast cancer [1,9,10]. It has been suggested that breast carcinoma patients who were in the highest quartile of BMI were 2.5 times as likely to die of their disease within 5 years of diagnosis compared with women in the lowest quartile of BMI [11].

Trastuzumab, a monoclonal antibody against HER-2 (also called CerbB2 or neu), has shown survival benefits in patients with HER-2-positive early and metastatic breast cancer [12]. HER-2 over expression is correlated with poorly differentiated, high-grade tumors and lymph node involvement [13,14]. HER-2 positive breast cancer patients have a worse prognosis than HER-2 negative breast cancer counterparts.

The aim of this study was to retrospectively evaluate the association between BMI and recurrence of breast cancer in HER-2 positive patients as related to adjuvant trastuzumab treatment.

Materials and methods

Medical records of female patients with AJCC stage 1-3, HER-2 positive breast cancer who applied for treatment to Oncology Outpatient Clinic, School of Medicine, Pamukkale University and Denizli State Hospital between March 2001 and March 2010 were retrospectively examined. HER-2 positivity was confirmed by either immunohistochemical and/or FISH analysis.

Weight/height measurements, detailed treatments and histopathological data of tumor were recorded to SPSS 17 pack software. BMI values of patients were classified as obese (BMI ≥30 kg/m^2) and non-obese according to World Health Organization (WHO) criteria. The WHO defines BMI classes as underweight (BMI <18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). For the purposes of the current analysis and because of the low number of patients, the underweight, normal and overweight BMI classes were categorized as “non-obese”.

BMI was computed by dividing the weight in kilograms by the square of the height in meters. BMI groups (obese or not) were analyzed using the Pearson chi-square test for categorical variables. All statistical analyses were performed with SPSS.17 software pack. Univariate proportional hazards models were used to examine associations between potential confounders and the time-to event endpoints. The influence of baseline factors on treatment effects was assessed by testing for interactions with treatment in Cox proportional hazards models for recurrence free survival (RFS). Covariates included hormone receptor status (ER and/or PR positivity) tumor size, presence of carcinoma in situ, BMI, trastuzumab therapy, number of metastatic lymph nodes, menopausal status and tumor grade. Kaplan-Meier curve for RFS was constructed and compared using the log-rank test. All analyses were by intention to treat. All *p* values and CIs were two sided. P values below 0.05 were considered significant.

Results

Among HER-2 positive 170 patients, 129 had accessible data and 114 with recorded weight / height measurements were statistically analyzed. Median age for all patients was 49 years (range 27-78). Chemotherapy was not administered to 7 patients. Forty two patients received anthracycline + trastuzumab and 77 patients received anthracycline + taxane + trastuzumab, while 3 patients received CMF regime. When trastuzumab was given, it was administered following chemotherapy. Of patients, 43 subjects did not receive radiotherapy. All patients examined for BMI had received chemotherapy. Characteristics features of obese and non-obese patients, as indicated by BMI values, are given in Table 1.

Table 1. Patient characteristics by body mass index (BMI) category

Characteristic	**BMI ≥ 30 kg/m²**	**BMI< 30 kg/m²**	***p***
Mean age (years)	51.1±9.3	48.8± 10.9	0.236
	No. of Patients (%)	No. of Patients (%)	
All patients	46 (40)	68 (60)	
Menopausal status			
Premenopausal	28	46	0.737
Postmenopausal	18	22	
Tumor size			
≤2 cm	25	39	0.433
>2cm	21	29	
Grade			
1/2	14	31	0.374
3	15	22	
Unknown	17	15	
No. of involved lymph nodes			
0	16	13	0.106
≥1	30	55	
Lymphovascular Invasion			
Yes	12	18	0.628
No	18	29	
Unknown	16	21	
Carcinoma insitu			
Yes	21	32	0.680
No	25	36	
Hormon receptor positivity			
Yes	17	43	0.002*
No	28	25	
Unknown	1		
Stage			
I	7	12	0.735
II	11	17	
III	16	36	
Unknown	12	3	
Trastuzumab therapy			
Yes	35	60	0.639
No	11	8	
Recurrence			
Yes	8	12	0.659
No	38	46	

Patients were divided into 2 groups with regards to BMI. In the group with BMI ≥30 kg/m^2, hormone receptor negativity was significantly higher (p =0.002). There was no significant difference in-between the two groups as regard to other parameters.

In the group with BMI≥30 kg/m^2, ER negativity rate was increased 2.2 folds (OR, 95% CI 1.32-3.91, p =0.001).

Recurrence-free survival was 8.8 ± 6.5 months (95 % CI 75.4-100.9) in the group with BMI<30, while it was 78.09 ± 12.43 (95 % CI 53.72-102.45) in the group with BMI≥30 and the difference was not significant (p =0.32).

When univariate analysis was performed (Table 2), disease recurrence was found in 7 of 95 patients (7.4 %) receiving Trastuzumab and 13 of 34 patients (38.2%) not receiving Trastuzumab. The difference was significant HR 0.12(95% CI 0.046-0.362, p <0.001). Cox regression analysis showed that (Table 3), only the presence of carcinoma in situ was found to be significantly related with RFS (HR 0.44 (95% CI 1.05-34.28, p = 0.044).

When the patients were analyzed as regard to receiving (95 patients, 74 %) and not receiving (33 patients, 26%) trastuzumab therapy, a significant relationship favoring trastuzumab treatment in-between RFS and both tumor size (p =0.04) and hormone receptor positivity with (p =0.02) were detected. Moreover, in the hormone receptor negative group, the risk of recurrence was 7.6 folds (95% CI 2.38-24.8) higher, in the absence of trastuzumab treatment.

Median follow-up was 24 months (range 3-257) and recurrence was found in 20 patients (15.5 %). Five patients died during follow-up. Mean RFS was 89.1± 6.5 months (95% CI, 3-124 months) and overall survival was 213.6 ±18.5 months (95% CI, 117.2-250.0 months). Overall survival was not further analyzed since adequate follow-up period could not be reached.

Discussion

Endogenous sex hormones are regarded as an important risk factor in development of breast cancer [15]. Considering studies conducted on same subject in the literature, there are studies indicating both positive relationship [15-19] and no relationship [20, 21] with estradiol and breast cancer in postmenopausal patients. Data indicating increased risk with obesity in the development of postmenopausal breast cancer is present in literature [4,5]. There are not only studies indicating positive relationship between level of estrogen and BMI [22,25], but there are also studies indicating no relationship [26,27]. However, the condition that is valid for premenopausal patients is not clearIn current study, we aimed to examine the influence of obesity on prognosis of HER-2 positive breast cancer as regard to trastuzumab treatment.

We divided patients with early stage HER-2 positive breast cancer into two groups with regards the BMI score, including subjects with BMI≥30 kg/m^2 and with BMI<30 kg/m^2. A significant relationship was found only between hormone receptor positivity and BMI (p =0.002). Hormone receptor was positive in 38 % of patients in BMI≥30 kg/m^2 group and in 63% of patients in BMI<30 kg/m^2 group. On the contrary to finding of our study, obesity has stronger positive relationship with hormone receptor positivity in postmenopausal women [28, 29]. This can be related with low number of patients and bias in pathological examination.

The positive effect of adjuvant trastuzumab administration on survival of HER-2 positive breast cancer patients was shown with prospective studies and the agent was introduced to routine administration [30-33]. The only effective parameter in univariate analyses of our current study was the presence of trastuzumab treatment (p <0.001). When patients were re-examined in two groups including patients receiving and not receiving trastuzumab, the recurrence risk was increased 7.6 folds in non-treated patients particularly in hormone receptor negative group (95% CI 2.38-24.8). A significant relationship was present in-between RFS and both tumor size (p =0.04) and hormone receptor positivity with (p =0.02) No relationship was found between trastuzumab treatment and other histopathological features.

In Cox regression analysis, only the presence of carcinoma in situ was statistically significant (Table 3).

In tumours containing both IDC (Invasive Ductal Carcinoma) and DCIS (Ductal Carcinoma Insitu), it is unclear whether or not the IDC component arises directly from DCIS. Some studies showed DCIS as the precursor of IDC-DCIS based tumors according to immunhistochemistry or genomic data [34,35]. Other studies have reported differences between DCIS and IDC-DCIS [36]. These studies suggest that DCIS might not be a precursor of the invasive cancer. One recent study showed that IDC co-existing with DCIS was characterized by

Table 2. Univariate model results for recurrence free survival

Variable	No. of patients	No. of events	HR (%95 CI)*	*p*
Hormon reseptor status				
Positive	72	8	1.14(0.80-2.41	0.178
Negative	56	11		
Metastatic lymph nodes				
Yes	95	17	2.25(0.616-8.231)	0.276
No	34	3		
Tumor grade				
1 - 2	45	4	2.39(0.642-8.914)	0.210
3	37	7		
Carcinoma insitu				
Yes	55	10	1.17(0.737-1.871)	0.469
No	74	10		
BMI ≥30 kg/m^2				
Yes	46	8	1.24(0.438-3.311)	0.659
No	68	12		
Trastuzumab therapy				
Yes	95	7	0.12(0.046-0.362)	<0.001*
No	34	13		
Menopausal status				
Premenopausal	81	12	1.15(0.433-3.051)	0.779
Postmenopausal	48	8		

*HR indicates hazard ratio, CI, confidence interval

Table 3. Cox regression analysis results for recurrence free survival

	HR	%95 CI	*p*
Hormone receptor status (positive vs negative)	2.17	051-9.2	0.29
Tumor size (>2cm vs ≤ 2 cm)	1.41	0.2-8.8	0.70
Detection of carcinoma insitu (yes vs no)	0.44	1.05-34.28	0.044*
BMI (≥30 kg/m^2 vs <30 kg/m^2)	1.05	0.17-6.19	0.95
Trastuzumab therapy (yes vs no)	1.43	0.26-7.80	0.68
No. of metastatic lymph nodes (≥4 vs<4)	1.32	0.25-6.87	0.73
Menopausal status (pre- vs postmenopausal)	2.16	0.43-10.70	0.34
Tumor grade (3 vs 1-2)	0.45	0.11-1.8	0.26

lower proliferation and metastatic potential than pure IDC [37]. Moreover, HER-2 expression and ER expression tend to be inversely related. This finding suggests that mitogenic signaling is important. But authors emphasis that whether IDC-DCIS is a useful independent prognostic markır or not should be remain speculative. For that reason, it is too early to make a decision on this topic. Future work is to explore molecular explanations in natural history with molecular development and differences between DCIS and IDC-DCIS. The median follow-up time is too short to expect major differences in disease-free survival and overall survival in our study. We were unable to find any study that reported any association among DCIS-IDC, BMI, and

Trastuzumab therapy. Trastuzumab treatment of seventy six patients was completed and other patients were still receiving treatment when analysis was conducted. Potential limitations of this study are the possibility of detection bias, low number of patients and non-completion of trastuzumab treatment by all patients when analysis was conducted.

In current study, it was found that trastuzumab is effective in breast cancer patients to prevent the recurrence, particularly in hormone receptor negative patients. Effect of BMI on disease-free survival was not significant (p =0.659). Survival analysis was not conducted since adequate number of patients could not be reached.

We suggest that studies with larger patient populations would be conducted for analyzing the relationships among BMI, presence of carcinoma insitu and menopausal and hormone receptor status' in HER-2 positive breast cancer patients.

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