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İMPORTANCE OF Kİ 67 VALUE FOR PATHOLOGİC COMPLETE RESPONSE İN LOCALLY ADVANCED BREAST CANCER PATİENTS RECEİVİNG NEOADJUVANT CHEMOTHERAPY

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ABSTRACT

Neoadjuvant chemotherapy (NACT) improves overall survival and renders possible breast-conserving treatment in locally advanced breast cancer. Association of Ki-67 and pCR is controversial.181 patients who received neoadjuvant chemotherapy between 2010 and 2017 years, were scanned. We investigated association between Ki-67 levels obtained before NACT and pCRs after NACT.

Results : This study was enrolled 157 patients .The median age was 49 (25 –83) in stage 2 group and 52 (23 –76) in stage 3 group.In patients with stage 2 breast cancer(n=108), mean level of Ki-67 was 38,0 (1–90) and in stage 3(n=59), was 35(2 –95). There was no statistically significant correlation between Ki-67 levels and pCR in stage 2 and stage 3 groups (p=0.213, 0.533 respectively). The mean level of Ki-67 in patients with pCR was 33,0and in patients with non-pCR was 41 in stage 2 group. This difference was not statistically significant (p=0.079). In stage 3 group, the mean level of Ki-67 in patients with pCR was 44 and in patients with non-pCR was 31but this difference was not statistically significant (p=0.236).

Conclusion : There was no relation between Ki-67 and pCR in our study but conclusions in literature remain controversial and randomised controlled studies are needed to determine the relation.

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INTRODUCTION

Globally, breast cancer is the most frequently diagnosed malignancy. It is also the leading cause of cancer death in women worldwide (Siegel *et al.,* 2018). Most patients with non-metastatic breast cancer should receive neoadjuvant chemotherapy (NACT). The goal of treatment is to induce a tumor response before surgery and enable breast conservation. In a meta-analysis, by Mieog JS *et al.* demonstrated outcomes of NACT; compared with adjuvant chemotherapy reduced risk of radical mastectomy, increased risk of locoregional recurrence and equivalent overall survival and disesase free survival (DFS)(2). Mostly anthracycline based regimens used in neoadjuvant setting but non-anthracycline based regimens may be used. All of patients treated with NACT should undergo surgery. It is possible to determine the efficacy of NACT in a comparatively short time via therapeutic response, which lets tumor response to chemotherapeutic agents be monitored by this approach (Kim *et al.,* 2014). Pathologic complete response (pCR) is associated with improvement in DFS (Liedtke *et al.,* 2008 and von Minckwitz *et al.,* 2012). Miller-Payne histopatologic scoring system is used to assess the patholocig response by comparing cancer cellularity in core biopsy (before treatment) with the resected tumor (after treatment). pCR shows reduction in tumor cellularity higher than 90% and no residual invasive cancer (Ogston *et al.,* 2003). Many studies have evaluated effective predictors of the response to NACT but some of these conclusions remain controversial. Ki-67 is a nuclear protein expressed during all phases of the cell cycle, except G0, and its expression has been reported to be correlated with the tumor cell proliferation rate. Many studies have investigated immunohistochemical expression of Ki-67 as a prognostic and predictive marker for breast Cancer (de Azambuja *et al.,* 2007; Yerushalmi *et al.,* 2010 and von Minckwitz *et al.,* 2011).

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Some studies have reported that high levels of Ki-67 was associated with higher pCR rates (Keam *et al.,* 2011 and Li *et al.,* 2011). However, there was no significant relationship in other studies (Zhou *et al.,* 2008 and Wei *et al.,* 2007). Therefore, we aimed to evaluate the function of pretherapeutic Ki-67 level as a predictive marker for pCR in patients with breast cancer treated using NACT.

MATERIALS AND METHODS

This study was planned as a retrospective single center study. Medical informations were obtained from the archive files of patients who were treated neoadjuvant chemotherapy, between 2010-2017 years, for breast cancer in the medical oncology clinic of Istanbul Okmeydan education and research hospital. Disease staging was performed according to TNM 7. Ki-67 level was obtained from pathological reports of patients before first chemotherapy. The histological response for breast and axilla was assesed according to Miller-Payne grading system (MPG). SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics was given as number and percentage for categorical variables, average, standard deviation, minimum, maximum for numeric variables. Two independent group comparisons of the numerical variable were performed with the Mann Whitney U test when normal distribution condition was not achieved. Comparisons of categorical variables ratios in groups were made with Chi Square Analysis. Monte Carlo simulation was applied when conditions were not met. Statistical significance level of alpha was accepted as $p < 0,05$.

RESULTS

For this study, 191 patients files who received NACT between 2010 and 2017 years, were scanned. Pathologic responses of 157 patients were reached from archive files.

The median age of patients was 51 (min 23 – max 85). 108 patients (68.8%) were stage 2 and 49 (31.2%) were stage 3. The median age of patients with stage 2 disease was 49 (min 25 – max 83) and of patients with stage 3 disease was 52 (min 23 – max 76). Avarage tumor diameters were 27mm, 24 mm and 33 mm for general, stage 2 group and stage 3 group, respectively. There was statistically significant difference of tumor size between stage 2 and 3 groups (p=0.027). While, 48.8% of patients were post-menoupausal, 51.2 % of were pre-menoupausal (Table 1.) 57 of pateints (36.3%) were HER 2 positive, 35 (22.3%) of were triple negative, 49(31.1%) of luminal B and 16(10.2) % of luminal A. Histologically, 150 of patients had invasive ductal carcinoma (Table 1). Patients with pathologically complete response (pCR) according to Miller-Payne grading system, constituted 51(32.4%) of all patients. 78.4% of patients with pCR had stage 2 disease and of 21.5% had stage 3 disease. Complete pathologic response rate was statistically significant higher in stage 2 group than stage 3 group (p=0.001). İn subgroup analysis, pCR rates were 43.8%, 28.5%, 26.5% and 18.7% in HER 2 positive, Luminal B, triple negative and Luminal A groups, respectively.(Table 2). In patients with stage 2 breast cancer, median level of Ki-67 was 38,0 (min 1 – max 90) and in stage 3, was 35 (min 2 – max 95). There was no statistically significant difference of Ki-67 levels between two groups (Table 2). Also patients were grouped according to the Ki-67 levels. The number of patients in each groups were similar. In Her-2 group,the median level of Ki-67 in patients with pCR was 38,0and in patients with non-pCR was 38,0 (p=0.852). (Table 2) In luminal B group, the median levels of Ki-67 were 31and 32 in patients with pCR and non – pCR, respectively (p=0.802). (Table 2) In triple negative group the median levels of Ki-67 were 54 and 57 in patients with pCR and non – pCR, respectively (p=0.879). (Table 2)There was no statistically significant correlation between Ki-67 levels and pCR in stage 2 and stage 3 groups (p=0.213, 0.533 respectively).

Table 1. Patients characteristics

	n	%
Total number of patients	191	
Patients with pathology result	157	
Histological type		
Other histology	7	4.4%
Age	51	Range 23-85
Age (Stage II)	49	Range 25-83
Age (Stage III)	52	Range 23-76
Stage II	108	68.8%
Stage III	49	31.2%
Tumor diameter (All patients)	27 mm	Range 9-84
Tumor diameter (Stage II)	24mm	Range9-76
Tumor diameter (Stage III)	33mm	Range 9-84
Premenapousal	76	48.5%
Postmenapousal	81	51.5%
Biological subgroup		
HER2 positive	57	36.3%
Triple negative	35	22.3%
Luminal B	49	31.2%
Luminal A	16	10.2%

Table 2 .Ki 67 of those with pathological complete response and those without

		Pathological Response								
				pCR			Non pCR			
	Total(n)	Mean	Min-max	n	Mean	Median	n	mean	median	p
Stage II	108	38.0	1-90	40	33	25	68	41	37	0.079
Stage III	49	35	2-95	11	44	35	38	31	25	0.236
HER 2 poz	57	37	5-80	25	38	22	32	38	40	0.852
Triple neg	35	57	1-95	10	54	52	25	57	60	0.869
Luminal B	49	33	5-85	13	31	27	36	32	27	0.802

The median level of Ki-67 in patients with pCR was 25 (33,0±23,3) and in patients with non-pCR was 37.5 (41,7±23,8), in stage 2 group (Table 2.).

DISCUSSION

This was a retrospective analysis to determine the predictive effect of Ki-67 in patients with breast cancer treated by NACT. Liedtke C et al reported that pathological response of 1118 women with breast cancer who received NACT. Overall, 163 patients (15%) experienced pCR compared with 945 patients (85%) with residual disease. In multivariate analysis, increased pCR rates were observed for patients with triple negative breast cancer (TNBC) compared with non-TNBC (4). von Minckwitz G et al described pCR as a predictive marker for DFS in patients who treated with NACT (5) In the present study, patients with pathologically complete response (pCR) according to Miller-Payne grading system, constituted 55 (32.9%) of all patients (table1) and pCR rates were 43.8%, 28.5%, 26.5% and 18.7% in HER 2 positive, Luminal B, triple negative and Luminal A groups, respectively. Denkert C et al reported that a wide range of Ki-67 cut points between 3%-94% for pCR and the three groups of Ki-67≤15% versus 15.1 %-35% versus >35% had pCR rates of 4.2%, 12.8% and 29% (p<0,0005), this effect was also present in six of eight molecular subtypes (Denkert *et al.,* 2013). Daniele G et al reported that post-treatment Ki67 showed a significant inverse correlation with clinical response (Generali *et al.,* 2009). In another trial, Rui C et al reported thatarea under ROC curve (AUC) of Ki67 expression was 0.632 in luminal-type breast cancer (P < 0.001, 95% CI 0.565–0.686). On the contrary, the AUC of Ki67 expression were 0.508, 0.548, and 0.54 in luminal–HER2, HER2-rich, and triple-negative type breast cancer separately, demonstrating that Ki67 level according to biopsy specimen was ineffective in forecasting of therapeutic response among these subtypes (P = 0.869, P = 0.303, and P = 0.448, respectively) (Rui Chen *et al.,* 2018). In a trial by Kim et al. suggested that Ki-67 expression in breast cancer tissue may be an effective factor for predicting the response to neoadjuvant chemotherapy and, Ki-67 is a useful predictive factor for pCR, especially in patients with ER-negative and HER2-positive breast Cancer (Kim *et al.,* 2014). In a trial suggested that baseline elevated Ki67 expression and the ER-status were both associated with a greater chance of obtaining a pathological complete response at residual histology (Bottini, 2005). In a review presented high KI-67 was found to be associated with immediate pathological complete response in the neoadjuvant setting (Luporsi *et al.,* 2012). Although, Learn PA et al reported that Ki-67 level was not associated pCR in patients treated by NACT (Learn *et al.,* 2005). Also in another trial was no found relation between Ki-67 and pCR in neoadjuvant setting (von Minckwitz *et al.,* 2008). In the present study we found no association between Ki67 and pCR in any groups. There is a confusion in literature about predictive value of Ki-67 for pCR in neoadjuvan setting. Since randomised controlled studies are needed to determine the relation between Ki-67 level and pathological response.

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