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Are preoperative serum CA15-3 levels different in breast cancer subgroups?

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ABSTRACT

Purpose: Breast cancer classifies to 4 major subgroups according to immunohistochemistry staining features as Luminal A, Luminal B, human epidermal growth factor receptor 2 overexpression, and Triple Negative. Cancer Antigen15-3 (CA15-3) is used as a tumor marker in breast cancer while its value in early stage and in breast cancer subgroups is still controversial. In this study, we aimed to investigate that whether it is or not differences of the serum preoperative CA15-3 levels in early breast cancer subgroups.

Methods: We retrospectively investigated medical records of 751 breast cancer patients who admitted to Afyon Kocatepe University Department of Medical Oncology between January 2010 and December 2016. Total 361 patients were included in this study. The cut off value of Ki-67 was used as 20 to distinguish between Luminal A from Luminal B subgroups. Cutoff values of CA15-3 were evaluated as 25U/mL.

Results: CA15-3 levels were not significantly different according to clinical features. Molecular subgroups were similar in CA15-3 levels ($P = 0.666$). Elevated levels of CA15-3 $\geq$ 25 U/mL were found 34 patients (20.5%) in Luminal A, 15 pa-

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tients (28.3%) in Luminal B_1, 15 patients (20.3%) in Luminal B_2, 7 patients (25%) in human epidermal growth factor receptor 2 overexpressed and 9 patients (22.5%) in triple negative groups.

Conclusion: There was no relationship preoperative CA15-3 levels and breast cancer subgroups.

Introduction

Breast cancer is comprised of highly heterogeneous subgroups with different pathological, molecular, and genetic characteristics.[1] The survival outcomes and response, rates the treatment of these subgroups are different.[2] These subgroups were identified by gene expression profiling of DNA microarray analyses but, usage of this method for routine clinical practice was very difficult[3] immunohistochemistry staining (IHC) are used as a surrogate for DNA microarray analyses because of a simple, available, and inexpensive method in daily clinical practice. Breast cancer subgroups were classified into 4 major subgroups based on the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67 proliferation index as following; luminal A, luminal B (HER2− or HER2+), HER2 over expression, and triple negative (TN) which does not express any of these markers.[4,5] In this widely accepted classification, Ki-67 was the most important tool to distinguish between luminal A from luminal B subgroups.[4,5] But there are some important disagreements among guidelines in terms of using Ki-67.[6] American Society of Clinical Oncology guideline[7] does not recommend usage of Ki-67 because of methodological problems of its measurement and lack of standardization. In contrast, European Society for Medical Oncology (ESMO) guideline,[8] the St. Gallen Consensus Panel,[9] and the European Group on Tumor Markers Panel[6] recommend that using Ki-67 cautiously.

Cancer Antigen 15-3 (CA15-3) is a member of the family of mucin glycoproteins (MUC1)[10] which is widely used as a tumor marker in the management of patients with breast cancer.[11,12] MUC1 is overexpressed in breast cancer cells when compared to normal breast tissue[13] and detected in peripheral blood by CA15-3 assay. The increase of MUC1 expression on the cell surface may precipitate invasion and metastasis of cancer cells as the CA15-3 has a role of cellular adhesion and cell to cell interaction.[14,15] Elevated level of CA15-3 can be also detected in early stage although was reported mostly in metastatic breast cancer.[16] High levels of CA15-3 is detectable also in different carcinoma and benign disease.[17] Its main usage area is for monitoring response to therapy in metastatic breast cancer along with other clinical features and radiological imaging.[17] However, the value of CA15-3 in early stage breast cancer is controversial because of the lack of organ and tumor sensitivity and specificity.[10,17-21]

Our knowledge about the correlation of between preoperative serum CA15-3 level and breast cancer subgroups are very limited and controversial. Published studies have had conflicting results with the elevation of CA15-3 levels and luminal versus nonluminal subgroups. Although some studies have shown a relationship between elevated CA15-3 levels and ER and PR status, most studies have not reported differences between breast cancer subgroups.[11]

In this study, we aimed to investigate the variation of serum preoperative serum CA15-3 levels in early stage breast cancer subgroups.

Methods

We retrospectively investigated medical records of all breast cancer patients who admitted to Afyon Kocatepe University Department of Medical Oncology between January 2010 and December 2016. Demographic data, ERs, PgRs, HER2s, Ki-67s and CA15-3 levels at the time of diagnosis

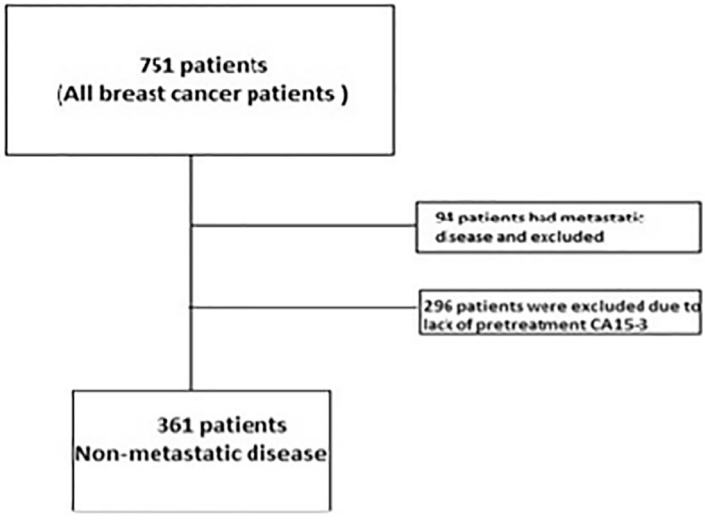

Fig. 1. Patient inclusion diagram.

were recorded. We investigated recordings of 751 breast cancer patients. 94 patients who had metastatic disease and 296 patients who had through lack of pretreatment CA15-3 levels were excluded. Total 361 patients were analyzed in this study (Fig 1).

CA15-3 levels were measured by immunoradiometric assay. CA15-3 values smaller than 25 U/mL were evaluated as normal. ER and PR positivity were considered as positive if ≥1% nuclear-staining tumor cells. Positive for HER2 were admitted either IHC HER2 3+ or fluorescent in situ hybridization amplified.The breast cancer were classified into 5 subgroups according to their IHC staining features[22] as follows: luminal A (ER+/PR+, HER2-−, and Ki-67 < 20%), luminal B_1 or Luminal B HER2− (ER+/PR±, HER2−, and Ki-67 ≥ 20%), luminal B_2 or Luminal B HER2+ (ER+/PR±, and HER2+), HER2 overexpression (ER−, PR−, HER2+) and TN type (ER−, PR−, HER2−).

Categorical variables were compared with chi-square test among groups. Distribution of the continuous variables for normality was checked with Kolmogorov-Smirnov test. Continuous variables were compared with Kruskal-Wallis test. All *P* values were 2-sided and <0.05 were accepted as statistically significant. Statistical analysis was made with SPSS 22.0 package programme.

The study was approved by the ethics committee at Afyon Kocatepe University Faculty of Medicine and carried out in accordance with Declaration of Helsinki principles and all applicable regulations.

Results

Clinicopathologic characteristics of the patients are given in Table 1. Median age of the study group was 54 years (min-max: 22-85). There were 166 patients (46%) in Luminal A, 53 patients (14.7%) in Luminal B_1, 74 patients (20.5%) in Luminal B_2, 28 patients (7.8%) in HER2 overexpressed, and 40 patients (11.1%) in TN group. Median CA15-3 was 18.75 U/mL (min-max: 0.4-62.04) in Luminal A, 19 U/mL (min-max: 6.59-35.48) in Luminal B_1, 17.05 U/mL (min-max: 1-84.7) in Luminal B_2, 16.9 U/mL (min-max: 8.6-32.21) in HER2 overexpression and 16.61 U/mL (min-max: 1.7-69.6) in TN groups. Molecular subgroups were similar to each other with regard to pretreatment CA15-3 levels ($P = 0.666$) (Fig 2). Also, elevated CA15-3 levels were not determined statistically significant differences according to age, histological types, tumor size, stage, grade, ER and/or PR status, and nodal status.

Table 1
Clinicopathologic characteristics of all patients.

SCharacteristic	Number of patients	CA 15-3 U/mLMedian (range)	*P*	CA 15-3 ≥ 25 U/mL	*P*
Age					
≥50	234	16.6 (0.4-69.6)	0.477	54/234	0.598
<50	127	17.86 (0.8-84.71)		26/127	
Histological type					
Invasive ductal	325	17.2 (0.4-84.71)	0.292	71/325	0.674
Other types	36	18.13 (10.5-43)		9/36	
Tumor size					
T1	92	18.03 (0.4-62.04)	0.07	26/92	0.07
T2	226	16.85 (1-59.43)		41/226	
T3	39	18.9 (4.6-84.71)		11/39	
T4	3	28.6 (21.11-43)		2/3	
Unknown	1				
Stage					
1	74	18.73 (0.4-37.46)	0.06	19/74	0.554
2	200	16.02 (1-59.43)		38/200	
3	87	19.16 (1.7-84.71)		23/87	
Grade					
1-2	205	18 (0.4-59.43)	0.328	45/205	0.07
3	106	16.33 (1-84.71)		16/106	
Unknown	50				
ER					
Positive	287	17.35 (0.4-84.71)	0.229	62/287	0.639
Negative	74	10,36 (1,7-69,6)		18/74	
PR					
Positive	261	17.13 (0.4-84.71)	0.176	59/261	0.779
Negative	100	17.5 (1.09-69.6)		21/100	
HR					
Positive	288	17.47 (0.4-84.71)	0.310	63/288	0.875
Negative	73	10.33 (1.7-69.6)		17/73	
Nodal status					
Negative	153	17.6 (0.4-59.43)	0.987	34/153	0.07
Positive	208	17.05 (1-84.71)		46/208	
Ki-67					
≥20	176	18.59 (1-69.6)	0.587	27/176	0.932
<20	185	18 (3.6-84.71)		18/185	
Molecular subgroups					
Luminal A	166	16.75 (0.4-62.04)	0.666	34/166	0.788
Luminal B_1	53	19 (6.59-35.48)		15/53	
Luminal B_2	74	17.05 (1-84.71)		15/74	
HER2	28	16.9 (8.6-32.21)		7/28	
TN	40	16.61 (1.7-69.6)		9/40	

Table 2
CA15-3 positivity rates according to molecular subgroups.

CA15-3 (U/mL)	Luminal A (n-%)	Luminal B_1(n-%)	Luminal B_2(n-%)	HER2 +(n-%)	TN(n-%)	*P*
≥25	34-20.5	15-28.3	15-20.3	7-25	9-22.5	0.788
<25	132-79.5	38-71.7	59-79.7	21-75	31-77.5	

Elevated levels of CA15-3 ≥ 25 U/mL were found 34 patients (20.5%) in Luminal A, 15 patients (28.3%) in Luminal B_1, 15 patients (20.3%) in Luminal B_2, 7 patients (25%) in HER2 overexpressed and 9 patients (22.5%) in TN groups. Groups were found similar regarding CA15-3 status ($P = 0.788$) (Table 2).

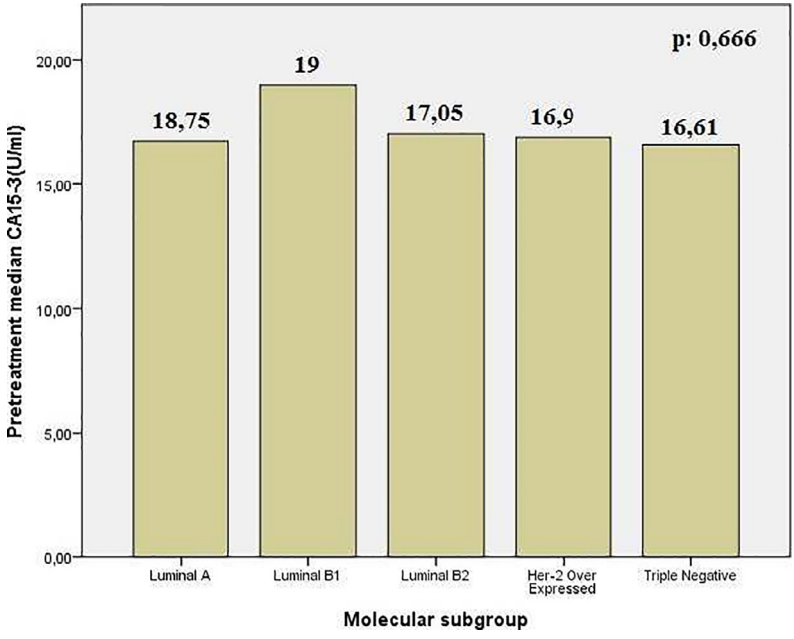

Fig. 2. Preoperative serum CA15-3 levels according to molecular subgroup.

Discussion

CA15-3 is still widely used as a tumor marker in the management of patients with breast cancer at the time of diagnosis, postoperative surveillance of asymptomatic women, and monitoring response to therapy in metastatic patients because it is an available, fast, cheap, easy, and quantitative test.[23] Previous studies have shown that elevated serum CA15-3 levels have more frequently observed in patients with metastatic breast cancer and its luminal subgroups.[3,11] These results are consistent with the hypothesis that overexpression of MUC1 is associated with ER expression (luminal subgroup) compared to nonluminal subgroups.[13] However, these studies which are including only metastatic patients have some conflicting results (Table 3). In a study of Park et al.,[3] increased CA15-3 level was not statistically different between TN and luminal subgroups although the luminal subgroup tended to have a higher level numerically (37.3% vs 45.6%, respectively). In contrast to this study, Yerushalmi et al.[11] showed that the lowest rate of elevated CA15-3 was in the TN subgroup (68.4%). CA15-3 level was found to be increased >80% of patients in luminal A and B groups and they have found statistically significant difference between luminal versus nonluminal subgroups (P <0.001).

Published studies which aimed to show the correlation of the serum preoperative CA15-3 levels and subgroups of breast cancer with early stage had more different results than metastatic status (Table 3). Only Li et al.[24] had found a statistically significant relationship ($P=0.015$) between the luminal A group and preoperative elevated CA15-3 levels. In contrast, Shao et al.[21] showed that in HER2+ (27.3%) and TN (18.9%) subgroups had a higher rate of elevated CA15-3 levels and this difference was statistically significant than luminal subgroups (8.8% in luminal A and 11.4% in luminal B, $P=0.012$). But, elevated CA15-3 levels were not found statistically different in the between luminal and nonluminal groups in studies of Kos et al.,[25] Nisman et al.,[16] and Wu et al.[26]

Nonstandard cutoff value was used in some studies and may be these preferences have affected the results. For example, ER and PR positivity were admitted as 10% by Wu et al.[26] while the American Society of Clinical Oncology/College of American Pathologists (CAP) Panel[27] and

Table 3
Studies of correlation between CA15-3 levels and breast cancer subgroups.

Author	Study year	Number of patients	Metastatic/ preoperative	Subgroups (%)	Ki-67(%)	The rates of elevated CA15-3	CA 15-3 cutoff value(U/mL)
Yerushalmi R. et al. [11]	2012	810	Metastatic	Luminal A (38.8%) Luminal B (30.9%) Luminal HER2+ (9.3%) HER2+ (7.6%) Basal type (10.4%) TN (nonbasal) (2.59%)	<14	**83.4** **86.8** **84.7** 75.0 69.3 68.4 $P < 0.001$	>28
Park S. et al. [3]	2012	536	Metastatic	HR+ (HER2−) (64.2%) HER2+ (ER−/PgR−) (16.8%) TN (19%)	Not reported	**45.6%** 24.4% 37.3% P <0.001	>28
Sandri MT. et al. [23]	2012	7942	Preoperative	Luminal A (29.6%) Luminal B HER2− (45.9%) Luminal B HER2+ (9.5%) HER2+ (nonluminal) (6.0%) TN (%9.1)	<20	Not reported	>31
Kos T. et al. [25]	2013	423	Preoperative (58 of the patients were metastatic at the time of diagnosis)	Luminal A (54.8) Luminal B (16.5) HER2+ (12.5) TN (16.1)	Not reported	48.1% 42.8% 26.0% 33.3% $P=0.11$	>31
Nisman B. et al. [16]	2013	159	Preoperative	Luminal A (52.2) Luminal B (20.7) HER2+ (nonluminal) (8.1) TN (18.8)	≤14	3.4% 18.1% 7.7% 10% $P=0.08$	>30
Wu S-g. et al. [26]	2014	470	Preoperative	Luminal A (ER+, PR+, HER2−) (55.7) Luminal B (ER+, PR+, HER2+) (15.3) HER2+,(ER−PR−) (15.5) TN (13.5)	≤25	10.3% 15.3 15.1 14.3 $P=0.513$	>25
Li H. et al. [24]	2014	368	Preoperative	Luminal A (22.5) Luminal B (51.4) HER2+ (9.0) TN (10.9) Unknown (6.2)	<14	**37.7** 27.3 21.4 (HER2+ and TN together) $P=0.015$	>13
Shao et al. [21]	2015	432	Preoperative	Luminal A (15.8%) Luminal B (56.9%) HER2+ (10.2%) TN (17.1%)	<14	8.8 11.4 **27.3** **18.9** $P=0.012$	>25

ESMO guideline[8] recommend that ≥1% of ER and/or PR expression should be considered positive. Also, Li et al. have selected cutoff value of CA15-3 as 13U/mL in their study.[24] In contrast, CA15-3 cutoff value was preferred as ≥25 U/mL in the other studies and it was ranged 25-31.

Ki-67 is the most widely used proliferation marker in breast cancer.[28] Petrelli et al.[29] have shown in a meta-analysis that high Ki-67 level was generally associated with clinically more aggressive behavior and poor outcome. There is no clearly standardized cutoff value for Ki-67, although it is commonly used in many countries to distinguish luminal A and luminal B_1.[6,9,30] Cutoff value of Ki-67 as 14% was recommended in previous studies.[4,5] However, ESMO[8] and St. Gallen International Expert Consensus 2013[22] report suggested a new cutoff value of Ki-67 as 20% instead of old cutoff value. Disagreement continues between 10% and 30% Ki-67 levels, although below 10% is considered low and above 30% is considered high.[9]

Studies which investigate the variation of between preoperative CA15-3 levels and subgroups of breast cancer had been performed in before 2015 years. Therefore, old cutoff value of Ki-67 was commonly used. Only, Wu et al.[26] admitted a different cutoff point of Ki-67 (as 25%) for their study. Even so, they could not show any statistical difference among breast cancer subgroups.

In 2006, Martin et al.[31] performed a study to evaluate the prognostic value of preoperative serum CA15-3 level in breast cancer. This study did not establish any relationship between CA15-3 levels and hormone receptor status. Similar to the reported by Martin et al., Sandri et al.[23] could not find a correlation between ER and PR status and preoperative serum CA15-3 levels in 7492 patients with breast cancer. However, CA15-3 level was associated with HER2 expression and the other prognostic factors such as age, tumor size, nodal status, Ki-67, histological grade, and perivascular invasion.

In our study, the cutoff value of Ki-67 was used as 20% consistent with the new recommendation of St. Gallen. ER and PR positivity were considered as positive if ≥1% nuclear-staining tumor cells. Cutoff values of CA15-3 were evaluated as 25 U/mL. Statistical analysis revealed that there were no differences between elevated preoperative CA15-3 levels and subgroups of breast cancer. Preoperative CA15-3 levels were not associated with ER and/or PR and HER2 expression.

Our study had some limitations. The study was followed retrospectively and so we could not found data of all breast cancer patients. Also, pathologic specimens were evaluated in the different center. Therefore, IHC staining results may not be homogenous because of methodological problems.

In conclusion, the positive correlation has been shown between MUC 1 overexpression and ER expression in patients with metastatic breast cancer in previous studies. [13-32] But this correlation was not found for early stage disease. Our study results are similar to the other prior reported studies. To date, it is not clarified that question of why elevated levels of CA15-3 is not different among subgroups of early stage breast cancer.

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