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Research Article

Importance of Prognostic Nutritional Index in Patients with Metastatic Breast Cancer Treated with Trastuzumab Emtansine

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Abstract

Objectives: Trastuzumab emtansine(T-DM1) is more effective in some patients. However, predictive factors are not clear for T-DM1 efficacy. We attempt to explore prognostic importance of albumin to alkaline phosphotase ratio (AAPR) and prognostic nutritional index (PNI) importance in patients who used T-DM1.

Methods: The present retrospective study included the sixty-one human epidermal growh factor-2 (HER-2) positive metastatic breast cancer patients who used T-DM1. The median values were used to analyze AAPR and PNI threshold. PNI and AAPR were measured at baseline and after one cycle. Survival analysis was performed by using Kaplan-Meier method and compared with log rank test. Univariate and multivariate analysis were performed to determine independent prognostic predictor of progression-free survival (PFS) and overall survival (OS).

Results: The optimal cutoff value for AAPR and PNI were 0.41 and 45.0, respectively. OS and PFS were obviously inferior in patients with AAPR<0.41 compared to patients with AAPR≥0.41 according to Kaplan-Meier curve (OS: p=0.028, PFS: p=0.047). Patients with PNI <45 prominently demonstrated poor OS and PFS than those with PNI≥45 according to Kaplan-Meier curve (OS: p=0.033, PFS: p=0.071).

Conclusion: Pretreatment PNI is reliable prognostic indicators in patients with mBC treated by T-DM1.

Keywords: Albumin to alkaline phosphotase ratio, overall survival, prognostic nutritional index, trastuzumab emtansine

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Breast cancer is the most common cancer among women. Despite the avaliability of effective treatment modalities such as chemotherapy, radiotherapy, surgery and targeted therapy, it remains the second most common cause of death in women.[1] Human epidermal growth factor-2 (HER-2) receptor positivity has been reported in 15-20 % in of all breast cancer patients , with aggressive tumor biology.[2] Extended progression free survival has been demonstrated among patients using trastuzumab, pertuzumab and chemotherapy combination therapy which are applied as the first line treatment.[3] However, there are a few effective agents in the second and third line, one of them is trastuzumab emtansin (T-DM1). T-DM1 is an antibody-drug conjugate and consisting of DM-1 and trastuzumab. Overall survival (OS) and progresion free survival (PFS) have been reported to be better in patients taking T-DM1 in

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EMILIA and TH3RESA studies. The overall response rate and OS were longer in patients with having high HER-2 mRNA concentration rates in the EMILIA study.[4] Moreover, Müller et al.[5] established which T-DM1 induced anti-tumor immunity in patients using T-DM1 under neoadjuvant therapy.

Cancer may affect the nutritional status, musculoskeletal system, and metabolism of the patient. The albumin to alkaline phosphatase ratio (AAPR) is defined as a serum albumin level divided by to alkalin phosphatase level . It was studied in patients having hepatocelluler carcinoma (HCC) in the year 2015 for the first time.[6]

The prognostic nutritional index (PNI) is a simple index reported by Ondera et al. PNI is calculated with blood lymphocyte and albumin count. PNI reflects both the inflammatory situation and the nutritional situation of the patients. These authors showed that patients with low PNI levels had a poor prognosis.[7] The relationship between survival and PNI was researched in different cancers such as breast, colorectal, lung and gastric cancer. Low PNI level has been related to poor prognosis in several studies.[8,9]

We have investigated whether PNI and AAPR have prognostic importance in patients who got T-DM1 in our study and this is the first study that has been performed on this subject.

Methods

A total of 61 patients who used T-DM1 and were diagnosed HER-2 positive mBC were between December 2017 and December 2020 were included in this study. Patients who discounted treatment after first cycle or patients with insufficient clinical data were excluded from the study. Patients data were recruited retrospectively. Patient age, menapouse status, previous anti HER-2 treatment, progression time, death time, metastasis side were enrolled. HER-2 status was verified with an immunohistochemical score (IHC) of 3 positive or a positive in situ hybridization test for those with an score of 2 according to American Society of Clinical Oncology/College of American Pathologists HER2 testing in breast cancer guidelines.[17,18] If there were at least 1% positive tumor cell nuclei in the sample that was evaluated by IHC, we have evaluated as hormone receptor- positive. Computer tomography and PET BT were performed to patients for detecting metastasis. Patients who have systemic chemotherapy in the last one month, heart failure, active inflammation, liver disease, bone disease and inflammatory disease were not included in this study. Deadline for the follow up is 30 december, 2020.

The alkaline phosphatase, albumin and lymphocyte count were recorded before the treatment of patients who got T-DM1. AAPR and PNI count of the patients were computed before treatment. PNI was computed as (total lymphocyte countx0.005) +(10xalbumine). AAPR was obtained by subdividing of the albumine to alkaline phosphotase. Because PNI is parametric index, the cut off value was used as mean. Since AAPR is non paremetric index, the cut off value was used as median value. The cut off value was computed as 0.4 for AAPR and 45.0 for PNI

T-DM1 was administered intravenously at an initial dose of 3.6mg/kg every three weeks. T-DM1 was administered 3.0mg/kg to patients who had adverse events. Denosumab or zoledronic acid were given to patients that have bone metastasis.

The chi-squared or Fisher exact tests were used to analyze the association between the clinical parameters and inflammation indexes including AAPR and PNI. Kolmogorov–Smirnov and Shapiro–Wilk tests, as well as graphical evaluations, were used to determine whether the quantitative data conformed to the normal distribution. Kaplan–Meier curves and the log-rank test were used to analyze the association between patient-related clinical parameters and survival time (OS and PFS). Overall survival (OS) was defined as the death occurs after the begining of the T-DM1 treatment. Progression free survival (PFS) was defined as the time from T-DM1 treatment to either first diesease progression or death. If the patients are still alive at last clinical evaluation, data were censored. Univariable analysis of the clinicopathological factors , AAPR and PNI were performed using a Cox proportional hazards model to obtain HRs and 95% CIs. All analyses were performed using SPSS software (version 22), and a P-value <0.05 was considered statistically significant.

Results

Sixty one patients were included in the study. Mean age was 54.0±13.0 of the patients. Twenty three patients were premenopausal and thirty seven patients were post menopausal. While fourty patients had estrogen receptor positivity, twenty patients estrogen receptor was negative. While 25 patients had positive progesteron receptor positivity, progesteron receptor of 36 patients was negative. HER-2 results of 48 patients were detected positive by immunohistochemical method. HER-2 score was 2(+) in 13 patients and that HER-2 positivity was detected by FISH method. While one or two metastasis site was detected in the 44 patients, more than two metastasis sites were determined in the 17 patients. While visceral metastasis was in 35 patients, it wasn t detected in 26 patients. Seventeen patients used pertuzumab and 21 patients used lapatinib. The rest of 23 patients got T-DM1 therapy after trastuzumab treatment. While primary tumor was removed in 41 patients, it

was not operated in 20 patients. The relationship of AAPR and PNI with clinicopathological variables is summarised in table 1. The statistically significant relationship was detected between AAPR with primary tumor surgery and menopausal status. There was not any association AAPR and PNI with other variables. The clinicopathological features of the patients were summarised in the table 1.

While overall survival 27.5 was months in patients under 60, It was 12.6 months in patients over 60 and difference was statistically meaningful (p=0.044). PFS detected as 4.0 months against 9.1 months and difference was not statistically significant (p=0.186) . OS and PFS were identified longer in premenapausal compared to postmenapausal but difference was not statistically meaningful (OS=31.0 vs15.2, PFS=9.7 vs6.0, p=0.063 for OS, p=0.398 for PFS). While overall survival was 31 months in patients who had one or 2 methastasis sites, it was detected 12.6 months for those having 3 or more metastasis sites and the difference was meaningful (p=0.006). While PFS was 9.1. months in patients having one or two metastasis side, It was detected 3.5 month in patients having three or more metastasis side and difference was not meaningful (p=0.076). OS and PFS was detected statistically significant longer in patients who

Table 1. Basic characteristic of the enrolled patients and relationship between AAPR or PNI and the patients outcomes

	n (%)	PNI			AAPR		
		<45.0	≥45.0	p	<0.41	≥0.41	p
Age							
<60, n	42 (68.9)	16	26	0.069	14	28	0.071
≥60, n	19 (31.1)	12	7		11	8	
Menopausal status							
Premenopausal	23 (37.7)	13	10	0.195	5	18	0.017
Postmenopausal	38 (62.3)	15	23		20	18	
Estrogen receptor status							
Positive	40 (67.2)	21	20	0.233	16	25	0.656
Negative	21 (32.8)	7	13		9	11	
Progesteron receptor status							
Positive	25 (41)	12	13	0.78	10	15	0.896
Negative	36 (59)	16	20		15	21	
HER-2 IHC status							
2+ with FISH positive	13 (21.3)	4	9	0.21	20	8	0.835
3+	48 (78.7)	24	24		5	28	
Number of metastatic sites							
1 and 2	44 (72.1)	18	26	0.20	19	25	0.574
3 and more	17 (27.9)	10	7		6	11	
Metastasis site							
Non visceral	26 (42.6)	9	17	0.127	10	16	0.73
Visceral	35 (57.4)	19	16		15	20	
Brain metastasis							
Present	12 (19.7)	7	5	0.33	7	5	0.173
Absent	49 (80.3)	21	28		18	31	
Surgery for the primary tumor							
Yes	41(67.2)	16	25	0.12	13	28	0.035
No	20 (32.8)	12	8		12	8	
Prior pertuzumab usage							
Yes	17 (27.9)	9	8	0.49	8	9	0.54
No	44 (72.1)	19	25		17	27	
Prior lapatinib usage							
Yes	21 (34.4)	11	10	0.46	16	24	
No	40 (65.6)	17	23	9	12	0.82	

PNI: prognostic nutritional index; AAPR: albumin to alkaline phosphatase ratio; OS: overall survival; PFS: progression free survival; FISH: fluorescence in situ hybridization.

have not visceral metastasis compared to the ones having visceral metastatis(OS=37.2 vs 18.8 month, PFS: 9.9 vs 5.5 month, p=0.033 for OS, p=0.006 for PFS). OS and PFS were statistically longer in patients who have surgery to primary tumor compared to patients not having surgery to primary tumor (p=0.024 for OS, p=0.002 for PFS). While OS and PFS were 11.5 and 3.0 months in patients who got pertuzumab treatment respectively , It was 27.5 months and 9.0 months in patients who did not get pertuzumab (for OS p=0.009, for PFS p=0.001). The cut off values of PNI and AAPR by inflammatory markers was found to be predictive for OS and PFS. While OS was 31.0 months in patients who have AAPR ≥0.41, It was detected 14.9 months AAPR<0.41(p=0.028. Besides, PFS was 9.7 months in patients with AAPR ≥0.41, It was found 6.0 months in patients with AAPR<0.41 (p=0.047). While OS and PFS was found 37.2 and 9.2 months in patients with PNI ≥45.0 respectively and It was 18.3 and 5.5 months with PNI <45.0 respectively (for OS p=0.033, for PFS p=0.072) The relationship of OS and PFS with inflammatory markers (AAPR and PNI) and clinicopathological features were summarised in the table 2.

Cox hazard ratio was used for revealing potential predictive factors. That OS was related to age subgroup, number of metastatic site, surgery primary tumor, prior pertuzumab

Table 2. Overall and progression-free survival times according to the clinical parameters, and PNI and AAPR scores

Parameters	Total (n)	Total (%)	OS (median)	p	PFS (median)	p
Age (years)						
<60	42	68.9	27.5±5.1	0.044	9.1±1.4	0.186
≥60	19	31.1	12.6±5.0		4.0±1.8	
Menopausal status						
Pre-	23	37.7	31.0±9.6	0.063	9.7±1.4	0.398
Post-	38	62.3	15.2±3.5		6.0±1.0	
HER-2 IHC status						
2+ with FISH positive	13	21.3	15.2±3.0	0.537	9.7±3.9	0.609
3+	48	78.7	26.4±4.6		7.6±1.3	
Number of metastatic sites						
1 and 2	44	72.1	31.0±9.0	0.006	9.1±1.3	0.076
3 and more	17	27.9	12.6±1.6		3.5±1.6	
Metastasis site						
Non visceral	26	42.6	37.2±3.8	0.033	9.9±1.7	0.006
Visceral	35	57.4	18.8±6.9		5.5±1.6	
Brain metastasis						
Present	12	19.7	27.5±6.6	0.049	3.1±1.7	0.84
Absent	49	80.3	13.5±9.3		9.1±1.8	
Surgery for the primary tumor						
Yes	41	67.2	27.5±5.4	0.024	9.7±1.5	0.002
No	20	32.8	12.6±2.1		2.9±0.2	
Prior pertuzumab usage						
Yes	17	27.9	11.5±5.9	0.009	3.0±0.5	0.001
No	44	72.1	27.5±5.7		9.7±1.1	
Prior lapatinib usage						
Yes	21	34.4	21.8±4.3	0.793	7.4±2.4	0.208
No	40	65.6	27.5±10.3		8.0±2.2	
PNI						
<45	28	46.0	17.8±5.5	0.033	5.5±2.4	0.071
≥45	33	54.0	37.2±12.5		9.2±1.5	
AAPR						
<0.41	25	41.0	14.9±3.6	0.028	6.0±1.7	0.047
≥0.41	36	59.0	31.0±4.2		9.7±1.5	
Overall	61	100	21.8±4.6		7.68±1.8	

PNI: prognostic nutritional index; AAPR: albumin to alkaline phosphatase ratio; OS: overall survival; PFS: progression free survival; FISH: fluorescence in situ hybridization.

usage, PNI and AAPR were found in the result of univariate analysis. Hazard ratio for age subgroup (HR=2.1 %95 CI: 1.0-4.6; p=0.049), for number of metastatic site (HR=2.7 95% CI:1.3-5.9; p=0.008), for surgery primary tumor (HR=2.4 95% CI 1.1-5.4; p=0.028), for prior pertuzumab (HR: 3.1 95% CI 1.2-7.9; p=0.013), for PNI (HR=0.45 95% CI 0.21-0.96; p=0.038), for AAPR (HR=0.42 95% CI 0.19-0.93; p=0.032) were detected in univariate analysis which was done for OS. The number of metastatic sites, prior pertuzumab usage and PNI were found meaningful in the multivariate analysis. Surgery to primary tumor, prior pertuzumab usage and AAPR were statistically found meaningful in the univariate analysis which was performed for PFS. Hazard ratio for surgery primary tumor (HR=2.6 95% CI 1.3-4.9; p=0.003), for prior pertuzumab (HR=2.9 95% CI 1.4-5.8; p=0.002), for AAPR (HR=0.5 95% CI 0.3-1.0; p=0.05) were detected in univariate analysis which was done for PFS. Prior pertuzumab usage and surgery primary tumor were found statistically significant in the multivariate analysis which was performed for PFS. Univariate and multivariate analysis of PFS and OS were summarised in the table 3.

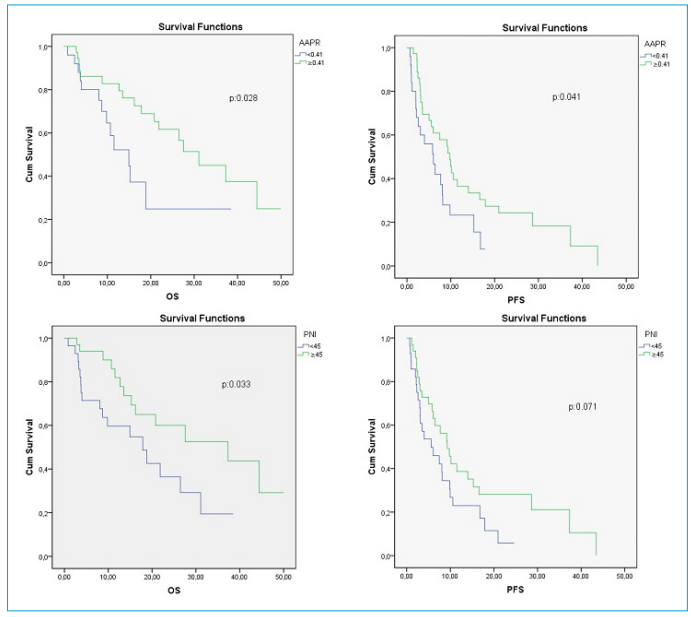

Figure 1. PFS and OS times according to PNI and AAPR.

Discussion

In the present study, we demonstrated that overall survival was better in patients who have high AAPR and PNI compared to patients having low AAPR and PNI. In the our study, PNI was found independent prognostic factor for OS and this was the first study about this subject in the literature.

The nutritional assumption and tumor related immune response are associated with tumor development and progression 6. That albumin regulates immune reactions, cell proliferation and DNA replication is exhibited in studies

Table 3. Univariate and multivariate analysis of factors that predicted progression free survival and overall survival among all patients

Parameters	Progression free survival			
	Univariate		Multivariate	
	Hazard ratio	p	Hazard ratio	p
Age subgroup	1.5 (0.8-2.8)	0.189		
Number of metastatic sites	1.7 (0.9-3.2)	0.079		
Surgery for the primary tumor	2.6 (1.3-4.9)	0.003	2.0 (1.0-3.8)	0.037
Prior pertuzumab usage	2.9 (1.4-5.8)	0.002	0.3 (0.1-0.7)	0.008
PNI	0.5 (0.3-1.0)	0.075		
AAPR	0.5 (0.3-1.0)	0.05	0.3 (0.09-1.5)	0.17
Parameters	**Overall survival**			
	Univariate		Multivariate	
	Hazard ratio	p	Hazard ratio	p
Age subgroup	2.1 (1.0-4.6)	0.049	1.9 (0.8-4.4)	0.12
Number of metastatic sites	2.7 (1.3-5.9)	0.008	2.7 (1.1-6.2)	0.01
Surgery for the primary tumor	2.4 (1.1-5.4)	0.028	1.6 (0.5-4.6)	0.33
Prior pertuzumab usage	3.1 (1.2-7.9)	0.013	0.3 (0.1-0.9)	0.03
PNI	0.45 (0.21-0.96)	0.038	0.9 (0.8-1.0)	0.05
AAPR	0.42 (0.19-0.93)	0.032	0.3 (0.04-2.3)	0.27

PNI: prognostic nutritional index; AAPR: albumin to alkaline phosphatase ratio.

which was performed11. In addition, it possesses antioxidant features against carcinogens. Therefore, nutritional deficiency, poor anticancer response and decreased immune response have been reported in cancer patients with low albumin count.[11] The level of ALP may be associated with malnutrition, bone disease, bile duct diseases and hepatitis. High ALP level is related to poor prognosis and heavy tumor burden has been demonstrated in different cancer types in the past studies.[12,13]

Furthermore,it has been reported that ALP causes inhibitory immune response effect. The relationship with micrometastasis of high ALP levels was reported by Mori et al. This situation indicates that cancer patients with a high ALP have a poor prognosis.[14] Meanwhile, ALP is expressed in cancer cells and is associated with tumor development.[15] The prognostic importance of AAPR has been demonstrated in studies performed in different cancer types such as hepatocellular cancer, nasopharyngeal cancer.[16,17] Moreover, low AAPR value has been associated with poor OS in patients without metastatic breast cancer in a study performed by Long et al.

T-DM1 is applied in HER2- positive metastatic breast cancer treatment. The significant association between HER2-expression level and T-DM1 treatment efficacy already has been established. T-DM1 has a more favorable effect on OS than on PFS in patients.[18] That T-DM1 is more effect on OS may not solely related to HER2 overexpression and other factors which are responsible from this process may be present.

Tumor-infiltrating lymphocyte (TIL) is a useful indicator for an immune reaction against cancer cells. A significant association between OS and TIL has been shown in the CLEOPATRA study. The result of this study data indicated that the efficacy of pertuzumab, a anti-HER2 drug, treatment is effective through the immune system in breast cancer.[19] However, there is insufficient data on whether the response induced by T-DM1 is associated with the immune system. Nevertheless, a past study indicated that the efficacy induced by T-DM1 may occur via the immune system in tumor-bearing mice 5.

We initially investigated the relationship between AAPR and clinicopathological features and found that primary tumor surgery and menopause status were related. In our study, a low AAPR was associated with poor OS and PFS, and the difference was statistically significant. Low AAPR level influences anticancer features and immunological functions. AAPR may provide an idea to clinicans about which patients can potentially benefit from this treatment.

The nutritional and immunological situation is related to prognosis.Various indices have been used for this purpose and with the most common one being PNI.[20] The lymphocyte count may reflect immune reaction or immunity against cancer cells.[21] Low PNI is related to low lymphocyte count or albumin level. The serum albumin level is an important parameter for determining the nutritional status. PNI is used as a prognostic index in several solid tumors. Low PNI value is related to poor prognosis.[22] OS has been reported longer in patients with high PNI value has been shown in patients diagnosed with osteosarcoma in a study performed by Xin et al. The OS and PFS were determined high in patients with high PNI value compared with those low PNI value in our study. The difference between OS was found to be statistically significant but not for PFS. Furthermore, no relation was noted among the clinicopathological features of patients who received TDM-1 therapy with PNI.

Our study was have some limitations. First, we accepted median value for cutoff value AAPR and PNI. Second, our study was retrospective and number of patients who were included to study were less. There is the necessity to studies that were performed with the large-scale patient population.

Conclusion

PNI was related to OS according to multivariate analysis in patients treated with T-DM1 therapy. A low PNI was predicted poor prognosis compared to high PNI group. OS and PFS were longer in patients with high AAPR compared to those with low AAPR but ıt was not found meaningful in multivariate analysis. However, larger scale, multicentre and prospective studies are required for affirm the prognostic importance of AAPR and PNI in these patient population.

Disclosures

Ethics Committee Approval: This study was approved by the ethics committee of Adana City Training and Research Hospital (2020/1078).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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