Research Article

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Is monitoring mean platelet volume necessary in breast cancer patients?

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Abstract: Background: Mean platelet volume (MPV) is a parameter that increases during thrombotic and cardiovascular events. Tamoxifen (Tmx) and aromatase inhibitors (AIs), which are adjuvant endocrine therapies, may cause serious side effects, such as vascular thrombosis. The present study investigated the changes in MPV values of breast cancer patients receiving long-term adjuvant hormone therapy and the relationship of MPV with adverse effects of hormonotherapy.

Methods: Data of 261 patients who had pathologically confirmed estrogen or progesterone receptor positive invasive breast cancer and had received hormonotherapy for at least a 5-year period were retrospectively analyzed. MPV levels were measured at baseline and at the first and fifth year of hormone therapy.

Results: All patients were females and their median age was 50 years (range, 27–78 years). The mean MPV value was significantly increased in all patients in the Tmx, AI, and switch groups over time ($p<0.001$).

Conclusion: This is the first study evaluating the relationship between the 5-year adjuvant endocrine therapy and changes in MPV values in breast cancer patients. Monitoring changes in MPV values may be predictive for severe side effects in breast cancer patients receiving hormone therapy.

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Keywords: Breast cancer; Tamoxifen; Aromatase inhibitors; Mean platelet volume; Side effect

1 Introduction

Most breast cancer patients are hormone receptor positive at diagnosis [1]. Five to ten years of adjuvant endocrine therapy, such as tamoxifen [Tmx] and aromatase inhibitors [AIs], is recommended for all hormone receptor positive early stage breast cancer patients [2, 3]. Tmx is a selective estrogen receptor modulator that binds to hormone receptors. AIs reduce the conversion of androgens to estrogens [4].

Platelets are blood components that have an important in hemostasis [5] as well as in thrombus formation and in the pathogenesis of atherosclerosis. Various genes, diseases, risk factors, and treatments affect platelet activation [6, 7]. Numerous studies have identified the role of platelets in the thrombosis process [8]. Large platelets have higher metabolic and enzymatic activities and are potentially more susceptible to thrombosis [9, 10]. Some large platelets are observed after coronary vascular events, and platelet size is a predictive marker for myocardial infarction and death [11].

Platelet size and density may vary from person to person. Mean platelet volume (MPV) is frequently used to measure volumetric platelet size, which is considered a potential indicator of platelet reactivity [9, 10]. Many studies have suggested that a high MPV value is one of the risk factors for vascular diseases. A high MPV value can also be expected as a result of vascular thrombotic events, such as myocardial and cerebral infarction [11-14].

Tamoxifen and AIs have several side effects. Although Tmx is associated with increased incidence of deep vein thrombosis and endometrial cancer, which is due to partial agonistic effect of estrogen, the underlying cause of thrombovascular side effects has as yet not been clearly

explained [15-19]. Cardiovascular events are relatively rare and serious side effects that are likely to be associated with AIs; however, they are more common than that observed in patients receiving Tmx [20, 21]. Although using AIs is associated with increased risk of fracture and musculoskeletal and genitourinary symptoms due to estrogen deprivation, potential adverse effects of AIs on cardiovascular events remain unclear [22-24].

The relationship of MPV and platelets with cardiovascular and thrombotic events and their prognostic role have been demonstrated in many cancers. However, the long-term effect of hormone therapy on MPV changes and the predictive role of MPV in thrombotic side effects have not been comprehensively studied in breast cancer. Karagoz et al. [25] investigated the effect of hormone therapy on MPV in a one-year period and demonstrated increased MPV levels in the patients receiving Tmx but no significant increase in MPV level of the patients receiving AIs. The aim of the present study was to evaluate the changes in MPV values in breast cancer patients receiving long-term adjuvant hormone therapy and the relationship of MPV with adverse effects of hormonotherapy.

2 Materials and methods

2.1 Patient selection

This retrospective study included patients with breast cancer who were admitted to the Medical Oncology Clinic of Izmir Ataturk Training and Research Hospital between 2006 and 2010. Data from 261 patients with pathologically confirmed estrogen or progesterone receptor positive invasive breast cancer who had received a hormonotherapy for at least a 5-year period were analyzed. The local Ethics Committee approved the study and written informed consents of the patients were obtained.

Patients who received Tmx (20 mg/day), anastrozole (1 mg/day), or letrozole (2.5 mg/day) or those who received Tmx and then switched to anastrazole or letrozole for at least a 5-year period, were included. Patients with inadequate follow-up, those with metastatic disease at the time of diagnosis, or those who developed metastasis during the follow-up period were excluded. Patients with chronic infection (autoimmune diseases, hepatitis, tuberculosis), chronic hematologic diseases, and chronic vascular diseases (cerebrovascular diseases, deep vein thrombosis) and patients using regular anticoagulants, anti-aggregants, and non-steroidal anti-inflammatory drugs were also excluded.

2.2 Measurement of mean platelet volume

Complete blood counts were performed using an automation system with an impedance-based analyzer (CELL-DYN 3700). MPV levels were measured at baseline and at the first and fifth year of hormone therapy. MPV was measured after at least a one-month period following the patients' last chemotherapy or radiotherapy treatment.

2.3 Statistical analysis

Data were analyzed using the IBM SPSS Statistics for Windows, version 20.0. (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean and standard deviation or median (minimum-maximum), where appropriate. General characteristics of subgroups were compared using a one-way ANOVA test. Comparisons of repeated samples were analyzed using the general linear model repeated-measures procedure. The analysis was adjusted using an additional multivariate regression model for variables that might affect the MPV levels. For pair-wise comparisons among the three time points, Bonferroni correction was performed. A p value of <0.05 was considered statistically significant.

3 Results

All patients (n=261) were female; their median age was 50 years (range, 27–78 years). Of the patients, 131 (50.2%) were premenopausal and 130 (49.8%) were postmenopausal. Most of the patients (88.9%) received adjuvant chemotherapy; 73.6% of the patients presented with stage 1 or 2 disease. Baseline characteristics of the patients are shown in Table 1.

Based on the hormone therapy received, approximately half of the patients (48.6%, n=127) received AIs, 56 (21.4%) patients received Tmx, and 78 (29.9%) were in the switch group. There were significant differences among these hormone therapy groups in terms of age and menopausal status ($p<0.001$ for each); as expected, the patients receiving Tmx were younger and premenopausal. There were no significant differences among the hormone therapy groups in terms of histological type ($p=0.867$), clinical stage ($p=0.684$), and receiving adjuvant chemotherapy treatment ($p=0.814$). Characteristics of the patients in the hormone therapy groups are presented in Table 2.

Table 1: Baseline characteristics of the patients

Characteristic	All (N=261)
Age, years	50 (27-78)
Menopausal status	
Premenopausal	131 (50.2)
Postmenopausal	130 (49.8)
Histological type	
Invasive ductal	177 (67.8)
Invasive lobular	28 (10.7)
Mixt	35 (13.4)
Others	21 (8.0)
Clinical stage	
Stage 1	57 (21.9)
Stage 2	135 (51.7)
Stage 3	69 (26.4)
Adjuvant chemotherapy	
Yes	232 (88.9)
No	29 (11.1)
Hormonotherapy	
Tmx	56 (21.4)
AI	127 (48.7)
Switch	78 (29.9)

Data are presented as n (%) or median (minimum-maximum), where appropriate.Tmx, Tamoxifen; AI, Aromatase inhibitor; Switch, Tamoxifen → Aromatase inhibitor; Mixt, Invasive ductal+ Invasive lobular.

During the 5-year follow-up period, one thromboembolic event (1.78%) occurred in the Tmx group, and three cardiovascular events (2.36%) occurred in the AI group. No cardiovascular or thromboembolic events were observed in the switch group.

The mean MPV level was found to be 8.09±0.08 fL at baseline, 8.33±0.08 fL in the first year of hormone therapy, and 9.6±0.07 fL in the fifth year of hormone therapy. The increase in the MPV values over time and the mean MPV values adjusted for age, histologic grade, lymph node involvement, clinical stage, estrogen receptor-positivity, age at diagnosis, and tumor size are given in Table 3. The MPV values at baseline and at the first and fifth years of hormone therapy are shown in Figure 1A.

The mean MPV value in the Tmx group was 8.26±0.17 fL at baseline, 8.50±0.17 fL in the first year of hormone therapy, and 9.71±0.14 fL in the fifth year of hormone therapy ($p<0.001$). The mean MPV value in the AI group was 8.04±0.11 fL at baseline, 8.22±0.11 fL in the first year of hormone therapy, and 9.57±0.97 fL in the fifth year of hormone therapy ($p<0.001$). In the switch group, the mean MPV value was 8.07±0.14 fL at baseline, 8.42±0.14 fL in the first year of hormone therapy, and 9.61±0.12 fL in the fifth year of hormone therapy ($p<0.001$). The increase in the MPV values over time in the hormone therapy groups and the mean MPV values adjusted for age, histologic grade, lymph node involvement, clinical stage, estrogen receptor positivity, age of diagnosis, and tumor size are given in Table 4. The MPV values at baseline and at the first and fifth years of hormone therapy in the study groups are shown in Figure 1B.

4 Discussion

To the best of our knowledge this is the first study evaluating the effect of long-term adjuvant endocrine therapy on MPV. In the present study, the MPV changes were investigated in 261 patients receiving hormone therapy for a period of 5 years. The MPV value increased in the Tmx, AI, and switch groups in the long-term follow-up. The increase in the MPV values in the first year did not reach a statistical significance in the Tmx and AI groups, whereas the increase in the fifth year was statistically significant in all groups.

In a study conducted by Karagoz et al. [25], the MPV values before and after treatment were compared in a one-year follow-up period. They reported a significant increase in the MPV values in the patients receiving Tmx but no significant change in the patients receiving AIs. In the present study, only the MPV increase in the switch group was significant in the first year of hormone therapy; however, it should be noted that the switch group included also the patients receiving Tmx. The difference between the results of our study and those of the study by Karagoz et al. [25] may be attributed to the limited number of patients (20 patients in the Tmx arm and 26 patients in the AI arm) and the patients in the Tmx arm being postmenopausal and at advanced age in their study. Thus, the significant increase in the MPV value in one-year follow-up reported by Karagoz et al. [25] might be related to age.

Table 2: Characteristics of the patients in the hormone therapy groups

Characteristic	Tmx n=56	AI n=127	Switch n=78	p
Age, years	41 (27-62)	59 (39-78)	46 (35-76)	<0.001
Menopausal status				
Premenopausal	55 (98.2)	4 (3.1)	72 (92.3)	<0.001
Postmenopausal	1 (1.8)	123 (96.9)	6 (7.7)	
Histologic type				
Invasive ductal	36 (64.3)	85 (66.9)	56 (71.8)	0.867
Invasive lobular	7 (12.5)	13 (10.2)	8 (10.3)	
Mixt	10 (17.9)	16 (12.6)	9 (11.5)	
Others	3 (5.4)	13 (10.3)	5 (6.5)	
Clinical stage				
Stage 1	15 (26.8)	26 (20.5)	16 (20.5)	0.684
Stage 2	27 (48.2)	65 (51.2)	43 (55.1)	
Stage 3	14 (25.0)	36 (28.3)	19 (24.4)	
Adjuvant chemotherapy				
Yes	51 (91.1)	107 (84.3)	74 (94.9)	0.814
No	5 (8.9)	20 (15.7)	4 (5.1)	

Data are presented as n (%) or median (minimum-maximum), where appropriate.
Tmx, Tamoxifen; AI, Aromatase inhibitor; Switch, Tamoxifen → Aromatase inhibitor; Mixt, Invasive ductal+ Invasive lobular.

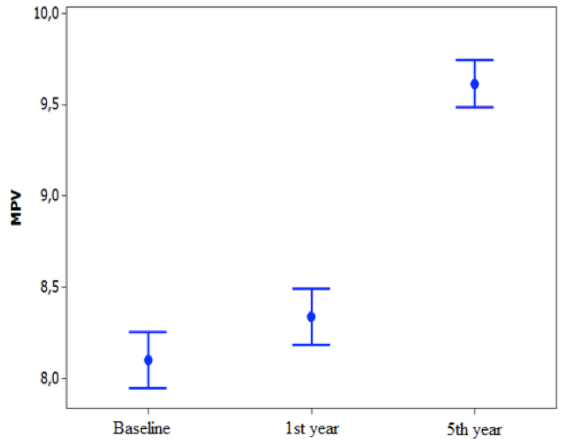

Figure 1A: Mean platelet volume (MPV) at baseline and at the first and fifth years of hormone therapy in all patients

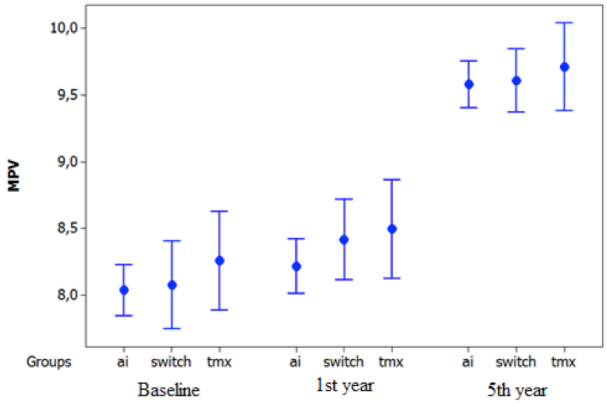

Figure 1B: Mean platelet volume (MPV) at baseline and at the first and fifth years of hormone therapy in the study groups

The relationship of MPV with thrombosis and inflammation has been demonstrated in many studies. In their study, Braekkan et al. [26] evaluated the interaction between MPV and venous thromboembolism in a total of 25,923 patients and reported unprovoked events (deep vein thrombosis and pulmonary embolism) to be 1.5 times more frequent in the group with high MPV values. In a meta-analysis including 16 studies, Chu et al. [27] analyzed the relationship between MPV value and incidence of acute myocardial infarction and found a relationship with high MPV values. Previous studies have shown that Tmx and AI may cause serious side effects such as cardiovascular events and thrombosis [22]. In the present study, the MPV value increased during the 5-year follow-up period in the patients receiving hormone therapy, which

Table 3: Change in the mean platelet volume in the patients by years

MPV values	Unadjusted	Adjusted*
At baseline	8.09±0.08[a]	8.08±0.08[a]
At the 1st year of hormone therapy	8.33±0.08[b]	8.34±0.08[b]
At the 5th year of hormone therapy	9.62±0.07[c]	9.62±0.07[c]
p	<0.001	<0.001

MPV, Mean Platelet Volume
Data are presented as mean± standard deviation.
* Adjusted for age, histologic grade, lymph node involvement, clinical stage, estrogen receptor-positivity, age at diagnosis, and tumor size
[a, b, c] denote the difference between the measurements. There is no difference in measurements where the letters are the same.

Table 4: Change in the mean platelet volume in the hormone therapy groups by years

MPV values	Unadjusted				Adjusted*			
	Tmx	AI	Switch	p	Tmx	AI	Switch	p
At baseline	8.26±0.17[a]	8.04±0.11[a]	8.07±0.14[a]	0.553	8.23±0.20[a]	8.06±0.14[a]	8.07±0.16[a]	0.781
At the 1st year of hormone therapy	8.50±0.17[a]	8.22±0.11[a]	8.42±0.14[b]	0.312	8.49±0.20[a]	8.23±0.14[a]	8.38±0.16[b]	0.680
At the 5th year of hormone therapy	9.71±0.14[b]	9.57±0.97[b]	9.61±0.12[c]	0.745	9.64±0.17[b]	9.63±0.12[b]	9.58±0.13[c]	0.942
p	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	

MPV, Mean Platelet Volume; Tmx, Tamoxifen; AI, Aromatase inhibitor
Data are presented as mean±standard deviation.
* Adjusted for age, histologic grade, lymph node involvement, clinical stage, estrogen receptor positivity, age of diagnosis, and tumor size.
[a, b, c] denote the difference among the measurements. There is no difference in measurements where the letters are the same.

might be related to serious side effects such as cardiovascular events and thrombosis.

The strength of the present retrospective study is its being the first study evaluating the MPV change in the patients receiving hormone therapy (Tmx, AI, and switch) for 5 years and investigating the relationship of MPV change with thrombotic side effects in these patients; therefore, it contributes to the current knowledge in the literature. Another strength of this study is that the results of our study regarding side effect ratios and patient characteristics are similar to the studies that involved a large number of patients and evaluated side effects of hormone therapy [28, 29].

The present study has several limitations. The first limitation is the small number of patients enrolled. The serious side effects due to hormone therapy were relatively rare in the present study; thus, it was difficult to detect an association between side effects and MPV. Moreover, due to the retrospective design of this study, unknown intervening factors might have influenced the results.

In conclusion, MPV increased due to hormone therapy in Tmx, AI, and switch groups in a 5-year follow-up period. It is known that MPV remains high in thrombotic and cardiovascular events. MPV may predict these side effects in breast cancer patients receiving hormone therapy; thus, MPV monitoring should be considered in these patients. Given the limited number of patients in the present study, further prospective large-scale studies are needed to better clarify the predictive role of MPV in the side effects associated with hormone therapy.

Conflict of interest statement: Authors state no conflict of interest

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