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The significance of Serum Vitamin D Levels on Changes in Hematological Parameters After Chemotherapy in Patients with Breast Cancer

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ABSTRACT

Objective: To investigate the relationship between serum Vitamin D (VD) level and the change of hematological parameters after chemotherapy in patients with breast cancer (BC) who received adjuvant Adriamycin and Cyclophosphamide (AC).

Material and Methods: A total of 74 BC patients who were treated with adjuvant 60 mg/m2 Adriamycin and 600 mg/m2 Cyclophosphamide (AC) were included in the study. VD levels, complete blood count (CBC) findings after 1st cycle AC were retrospectively recorded. The relationship between changes in CBC parameters according to VD levels and the presence of hematological toxicity was examined.

Results: The mean age was 55.11±9.97 years and the median VD level was 12.78 (4-53.40) ng/mL. In all patient groups, there was a significant decrease in the values of lymphocytes and monocytes after chemotherapy (p=0.030, p=0.024 respectively). In the correlation analysis, there was no correlation between VD levels and hemoglobin levels, the number of cells in CBC-1, and the amount of change in the number of cells in after chemotherapy. However, there was a negative correlation between VD level and platelet/lymphocyte ratio-1 (PLR-1), monocyte/lymphocyte ratio-1 (MLR-1) (p=0.025, r:-0.237; p=0.001, r:-0.370, respectively), but there was no correlation with PLR-2 and MLR-2 (p>0.05 all).

Conclusion: There was no relationship between VD levels and changes in hematological parameters and hematological toxicity related to AC chemotherapy in the patient with BC. VD level was inversely correlated with PLR-1 and MLR-1, which is generally accepted as inflammatory markers. This result showed that the levels of VD do not have a significant role in the development of hematological toxicity after AC chemotherapy in BC.

Keywords: Breast cancer, serum VD level, hematological toxicity, PLR, NLR, MLR

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INTRODUCTION

Vitamin D (VD) is a steroid hormone that regulates calcium and phosphorus metabolism (1). VD exerted important functions in tumor development by regulating cell proliferation, facilitating apoptosis, promoting cell differentiation, and inhibiting angiogenesis (2). Also, VD regulates the function of immune cells and the differentiation and proliferation of hematopoietic cells (3). Vitamin D Receptor (VDR) is expressed in many cell types, playing that it may have additional roles in other organs, including the hematopoietic system (4). 1,25(OH)2D3 promotes monocyte/macrophage as opposed to neutrophil development of normal myeloid progenitors. Moreover, it influences the early development of monocytes and invariant natural killer T cells and the further maturation of some immune cell types. Findings regarding the regulation of gene expression have revealed that there are links between the actions of VD and cytokines. These include influences on the production/action of the hematopoietic cytokines that are essential to the development and function of the blood cells (5).

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The 1,25(OH)2D3, the most biological active metabolite of VD, acts on T and B lymphocytes to modulate both the cytotoxic and antibody-producing functions of lymphocytes (6). Hematopoietic defects such as anemia, extramedullary hematopoiesis, thrombocytopenia, myelofibrosis and myelodysplasia were exhibited by children with VD deficiency-associated rickets (7). There is a strong linkage between inflammation and cancer. Cancer-related inflammation causes suppression of antitumor immunity by recruiting regulatory T cells and activating chemokines, which results in tumor growth and metastasis (8). Although the relationship between chronic inflammatory diseases and VD deficiency has been described in the literature (9). VD has now been convincingly shown both in vitro and in preclinical animal models to alter the differentiation, proliferation, and apoptosis of cancer cells. VD also shows anti-inflammatory, anti-oxidative, and immunomodulatory effects (10).

VD level is evaluated with serum 25(OH)D level. 25(OH)D indicates intake of VD and endogenous production. If 25(OH)D level is lower than 20 ng/mL, it is defined as VD deficiency, and between 21 and 29 ng/mL is defined as VD insufficiency. If it is higher than 30 ng/mL, it is defined as normal VD level and if it is higher than 150 ng/mL, it is defined as VD intoxication (11).

Neoplastic cells contain a VDR. When the 25(OH)D level exceeds 30 ng/mL, cancer cells make 1.25(OH)D via 1 alpha hydroxylase enzyme. 1.25(OH)D has a reducing effect on proliferation, invasion, angiogenesis, metastasis, and has an enhancing effect on differentiation and apoptosis. 1.25(OH)D collapses after it has completed its function in the cancer cell and cannot enter the circulation. Therefore, it does not affect calcium metabolism (12).

The platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) were used to determine inflammation in different types of malignancies, metabolic syndrome, infectious diseases, cardiovascular disease, end-stage renal disease, and other inflammatory diseases (13). Increased NLR, PLR levels indicate increased inflammation and are used as predictors of morbidity and mortality in systemic inflammation. NLR, PLR, and monocytes/lymphocyte ratio (MLR) are shown as new markers in the evaluation of systemic inflammatory response and are used to monitor the prognosis, morbidity, and mortality of many diseases (14). The NLR may act as a marker for the evaluation of the systemic balance between pro-tumor inflammation associated with neutrophils and antitumor immune response associated with lymphocytes. An increased NLR may indicate a trend for decreased antitumor immune capacity and increased pro-tumor inflammation. In another study, a higher NLR was associated with more advanced disease stage in younger patients. They found that an elevated NLR was associated with lymph node metastases and the depth of stromal infiltration (15). In a study, In patients with pancreatic cancer, NLR was found to be a more sensitive marker than PLR in determining the response to chemotherapy (16).

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death among females (17). 60 mg/m2 Adriamycin and 600 mg/m2 Cyclophosphamide (AC) is widely used in the adjuvant treatment of breast cancer. Cyclophosphamide is an alkylating agent. As cyclophosphamide is in clinical use for more than 40 years, there is a lot of experience using this drug for the treatment of cancer and as an immunosuppressive agent for the treatment of autoimmune and immune-mediated diseases (18). After using cyclophosphamide leukopenia develops 8 to 14 days after administration. Thrombocytopenia occurs but is rarely significant. Adriamycin is an antitumor antibiotic and effective in a large variety of tumors. One of the dose-limiting side effects of adriamycin is myelosuppression, especially leukopenia. The combination of adriamycin and cyclophosphamide has a greater myelosuppression effect (19). The occurrence of cytopenia's can cause delay or discontinuation of treatment. This situation affects cure rates negatively.

In light of the above-mentioned information's about the essential role of VD in the hematopoietic system and we investigated whether VD has any effects on hematological toxicity and changes in hematological parameters due to AC chemotherapy.

MATERIAL AND METHODS

The study included 74 women with BC who had surgery [(mastectomy or lumpectomy) + (sentinel lymph node dissection or axillary lymph node dissection)]. Sociodemographic data and blood tests of the individuals were obtained from the hospital automation system retrospectively. VD values are measurements within the last one month.

Complete blood count (CBC) values are measurements taken before the first chemotherapy cycle and before the second chemotherapy. It was investigated whether there were any changes that would make statistical difference in CBC results, NLR, PLR and MLR levels before and after treatment.

The relationship between these changes and the VD level was evaluated. VD status was classified as VD deficiency (<20 ng/mL) and non-deficiency (>20 ng/mL) according to Holick et all (20). Exclusion criteria were determined as follows, male patients, pregnant patients, patients with metastases, and parathyroid and thyroid diseases.

In the statistical analysis of the data, v.22.0 version of the IBM SPSS package program was used. In comparison between groups, paired samples test was used for normally distributed values and Wilcoxon signed rank test was used for non-parametric data. Categorical data were compared with chi-square test. Values with $p<0.05$ were considered statistically significant.

Approval was obtained from the local ethics committee for this study (Decision No: 2020/193).

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RESULTS

The mean age of the patients was 55.11 ± 9.97 years. Average diseases free survival was 26.3 (min:5-max:50) months. When VD level is considered as 20 ng/mL as cut off, in the group with low and high VD level, leukocyte-1, neutrophil-1, platelets-1, eosinophils-1, basophils-1, mean platelet volume-1, leukocyte-2, neutrophil-2, platelets-2, eosinophils-2, basophils-2, mean platelet volume-2 levels were similar (p>0.05; all). There was a significant decrease between lymphocyte-1, monocyte-1, and lymphocyte-2, monocyte-2 values after chemotherapy in all patient groups (p=0.030, p=0.024) respectively (Table 1).

There was no correlation between VD level, age, hemoglobin level, and the number of cells on CBC. However, there was a negative correlation between VD level and PLR-1, MLR-1 (p=0.025, r:-0.237; p=0.001, r:-0.370, respectively), there was no correlation with PLR-2 and MLR-2 (p>0.05 all) (Table 2).

There was no significant relationship between the amount of changes in CBC parameters after chemotherapy and VD level (p>0.05 all) (Table 3).

Table 1. The demographic features and complete blood count parameters of patients

	Variables	All patients (N= 74)	p*
Age (years), mean ± SD		55.11 ± 9.97	N/A
VD, ng/mL median (min – max)		12.78 (4 – 53.40)	N/A
Hemoglobin (g/dL), median (min- max)	Hb1 Hb2	12.61 ± 1.44 12.21 ± 1.43	0.000#
Leucocyte(10^3/mm^3) mean ± SD	Leu1 Leu2	7.28 ± 2 7.20 ± 2.98	0.801#
Lymphocyte(10^3/mm^3) median (min – max)	Ly1 Ly2	2.15 (0.6 – 4.8) 1.93 (0.35 – 4.54)	0.030*
Neutrophil(10^3/mm^3) median (min – max)	Neu1 Neu2	4.21 (1.67 – 8.83) 4.09 (0.42 – 17.6)	0.848*
Platelet(10^3/mm^3) mean ± SD	Plt1 Plt2	261.18 ± 67.81 259.71 ± 70.61	0.408#
Eosinophil(10^3/mm^3) median (min – max)	Eos1 Eos2	0.11 (0 – 2.61) 0.09 (0 – 0.58)	0.173*
Basophil(10^3/mm^3) median (min – max)	Baso1 Baso2	0.03 (0 – 4) 0.02 (0 – 0.11)	0.020*
Monocyte(10^3/mm^3) median (min – max)	Mono1 Mono2	0.43 (0.09 – 1.91) 0.37 (0.02 – 1.19)	0.024*
Mean Platelet Volume(fL) mean ± SD	MPV1 MPV2	10.34 ± 1.03 10.18 ± 1	0.063#
NLR (%) (min – max)	Neu1/Ly1 Neu2/Ly2	2.011 (0.76 – 5.93) 2.103 (0.26 – 16.94)	0.108
PLR (%) median (min – max)	Plt1/Ly1 Plt2/Ly2	120.76 (39.73 – 461.29) 132.75 (37.01 – 607.69)	0.024
MLR (%) median (min – max)	Mono1/Ly1 Mono2/Ly2	0.208 (0.03 – 0.81) 0.181 (0.01 – 0.98)	0.307
Stage, n (%)	II III	32 (43.2) 42 (56.8)	N/A

*Wilcoxon test, #Paired samples T test. SD, standard deviation; Hb1, basal hemoglobin level; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; MPV, mean platelet volume; PLT, platelet count; ELR, eosinophil/lymphocyte ratio; MER, monocyte/eosinophil ratio; Leu1, basal leucocyte count; Ly1, basal lymphocyte count; Neu1, basal neutrophil count; Plt1, basal platelet count; Eos1, basal eosinophil count; Baso1, basal basophil count; Mono1, basal monocyte count; MPV1, basal mean platelet volume Hb2, hemoglobin level after chemotherapy; Leu2, leucocyte count after chemotherapy; Ly2, lymphocyte count after chemotherapy; Neu2, neutrophil count after chemotherapy; Plt2, platelet count after chemotherapy; Eos2, eosinophil count after chemotherapy; Baso2, basophil count after chemotherapy; Mono2, monocyte count after chemotherapy; MPV2, mean platelet volume after chemotherapy.

Table 2. Changes in cytopenia and complete blood count according to VD deficiency

Variables		VD<20 ng/mL (n=58)	VD≥20 ng/mL (n=16)	p*
Decrease in Hemoglobin, n (%)	Yes No	36 (62) 22 (38)	8 (50) 8 (50)	0.278
Decrease in Basophil, n (%)	Yes No	32 (55) 26 (45)	8 (50) 8 (50)	0.465
Decrease in Eosinophil, n (%)	Yes No	31 (53.5) 27 (46.5)	10 (62.5) 6 (37.5)	0.362
Decrease in Lymphocyte, n (%)	Yes No	38 (65.5) 20 (34.5)	9 (56) 7 (44)	0.344
PLR Increase, n (%)	Yes No	25 (43) 33 (57)	6 (37.5) 10 (62.5)	0.458
Decrease in Monocyte, n (%)	Yes No	25 (43) 33 (57)	5 (31) 11 (69)	0.288

*Pearson Correlation test.

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Table 3. Relationship between VD levels patients with and without significant reduction after chemotherapy

Variables		N	VD levels median (min – max)	p*
Decrease in Eosinophil, n (%)	Yes	41 (55.4)	13.56 (4 – 53.40)	0.341
	No	33 (44.6)	12.18 (4.50 – 50.16)	
Decrease in Basophil, n (%)	Yes	34 (45.9)	12.47 (4 – 53.4)	0.854
	No	40 (54.1)	13.10 (4.50 – 50.16)	
Decrease in Hemoglobin, n (%)	Yes	44 (59.5)	12.78 (4 – 53.4)	0.467
	No	30 (40.5)	12.89 (4.50 – 50.16)	
Decrease in Lymphocyte, n (%)	Yes	47 (63.5)	12.8 (4 – 53.40)	0.225
	No	27 (36.5)	14.13 (6.45 – 50.16)	
Decrease in Monocyte, n (%)	Yes	44 (59.5)	13.78 (4 – 53.40)	0.269
	No	30 (40.5)	11.78 (4 – 35.05)	
PLR Increase, n (%)	Yes	43 (58.1)	12.23 (4 – 53.4)	0.437
	No	31 (41.9)	12.85 (6.85 – 50.16)	

* Mann-Whitney U test; PLR, platelet/lymphocyte ratio

DISCUSSION

This is the first study investigating the significance of serum VD levels in changes in hematological parameters after anthracycline-based chemotherapy in breast cancer patients. According to the data obtained in our study, the mean VD level in patients was determined as 12.78 (4-53.40) ng/mL and was under 20 ng/mL reported as a deficiency. The role of exposure to sunlight in VD synthesis is very important. Our study was conducted in locations situated at 41.20 north latitude and 32.60 east longitude in the north of Turkey. Studies have shown that those living in the north pole have a higher risk of getting certain types of cancer than those living in the south pole (**21**).

In a study, with 103 patients with BC, the average VD level was determined as 17 ng/mL. These results were similar to the results of our study (**22**). A meta-analysis showed a direct relationship between VD deficiency and breast cancer (**23**).

A negative correlation between VD level and PLR 1, MLR 1 (p=0.025, r: -0.237; p=0.001, r: -0.370; respectively) may indicate the presence of chronic high inflammation in patients with low VD levels. This may indicate that chronic increased inflammation is a risk factor for the development of malignancy. Cancer-related inflammation contributed to the proliferation of tumor cells, destroyed the adaptive immune response, and changed the effect of chemotherapeutics. Lymphocytes can eliminate tumor cells by inhibiting cell-induced cytotoxicity, proliferation and migration (**24**).

In a study, patients with breast cancer preoperative increased PLR found that worsening the prognosis (**25**). In the retrospective study in 2016, PLR and NLR in the general population were significantly higher in patients with low 25(OH)D levels. PLR and NLR were significantly associated with 25(OH)D levels, and PLR was found to be an independent predictor of 25(OH)D levels (**26**).

Increased PLR is a negative inflammatory marker in cardiovascular diseases and malignant conditions (**27**). PLR is seen as a predictor of mortality in heart, lung and some oncological diseases (**28**). There was no correlation between PLR-2, MLR-2 (p>0.05 all). This situation can be explained by the normalization of inflammatory markers due to the AC effect independent of VD level after AC administration. The change in CBC parameters after chemotherapy was found to be significantly lower between Lymphocyte-1, Monocyte-1 and Lymphocyte-2, Monocyte-2 values (p>0.030, p>0.024 respectively) and there was no significant difference in these parameters between low and high VD groups. This may have caused a significant difference in the study group, as the mean VD levels were close and the number of patients in the high VD group was low. In the correlation analysis, there was no relationship between VD levels between the PLR-1, PLR-2; NLR-1, NLR-2, and MLR-1, MLR-2 levels before and after chemotherapy. Narien et al. reported that the use of VD analogs before the application of antineoplastic agents can reduce hematological toxicity by modulating bone marrow and stromal cells (**29**). However in a study investigating the effect of NLR, PLR and MLR on the prognosis of BC, increased NLR and PLR were found to be important in prognosis, while MLR was not effective in prognosis (**30**). NLR and PLR are valuable prognostic biomarkers in most solid tumors but their value in guiding treatment management needs further research. Moreover, the prognostic values of these systemic inflammatory biomarkers need to be further confirmed in prospective clinical trials for various malignancies (**31**). Since death did not occur, we were unable to provide information about the effects of these parameters on overall survival. Further studies are also needed to explore the driving and regulatory mechanisms of the cancer-related systemic inflammatory response and to search for potential therapeutic targets for cancer population (**32**). Our study has some limitations. First, only one session of chemotherapy was used. In order to clearly understand the effect of vitamin D levels on hematological parameters and hematological toxity, it is necessary to see the changes in the following chemotherapy sessions. In addition, the study could be done with more patient participation.

CONCLUSION

There was no relationship between VD levels and changes in hematological parameters and hematological toxicity related to AC chemotherapy in patient with BC. VD level at the time of diagnosis was found to correlate negatively with PLR and MLR. This result showed that the levels of VD do not have a significant role in the development of hematological toxity after AC chemotherapy in BC. In order to understand the importance of VD levels in breast cancer prospective studies are needed.

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