



Research Article

Does Vitamin D Replacement Alter the Chemotherapy Outcome in Lung Cancer

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Abstract

Objectives: Lung cancer accounts for 20% of cancer-related deaths worldwide. Several studies have shown that Vitamin D levels at the time of diagnosis are prognostic in lung cancer. In this study, we evaluated the relationship between pre-diagnosis Vitamin D replacement levels and platinum-based chemotherapy results.

Methods: In this cross-sectional study, we retrospectively analyzed archive records of all 247 patients diagnosed with lung cancer from an oncology center in Turkey, between 2012-2018. The chemotherapy outcomes, Vitamin D levels and replacement doses of these patients up to 6 months ago were recorded.

Results: Vitamin D levels of 153 patients were below 15 ng/mL, 65 patients had a level of 15-30 ng/mL, and 29 patients had a vitamin D level higher than 30 ng/mL. In the study population, 215 had a replacement below 300.000 IU whereas 32 had a replacement above 300.000 IU. When the patients were evaluated based on their chemotherapy responses, no difference was observed between the patients with below and above 300.000 IU. In our study, Vitamin D and replacement level at the time of diagnosis did not change the chemotherapy response.

Conclusion: Vitamin D replacement levels were not significantly associated with chemotherapy outcomes in our study.

Keywords: Chemotherapy response, lung cancer, prognosis, vitamin D

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Lung cancer is one of the most common cancer types in many countries. The lung cancers are composing the 20% of the cancer deaths worldwide.^[1] Despite recent advances in lung cancer treatment, the five-year survival rates are still low, in the range of 10-30% in most countries.^[2]

Vitamin D is mainly produced by direct dietary intake or transformation with sunlight exposure in the body. These precursors are converted 25-OH Vitamin D in the liver.^[3,4] Most of the tissues have 1-alfa hydroxylase activity and also vitamin D receptors. Vitamin D is hypothesized to have an anti-cancer effect. Vitamin D may have a role in inhibiting cell proliferation, angiogenesis, invasion, and metas-

tasis.^[4-6] Epidemiologic studies have shown that vitamin D insufficiency is related to most human cancers.^[7,8] About this literature, the elevated circulating levels of vitamin D is proven to be related to a reduced risk of lung cancer.^[9,10] In another article, interestingly, the outcome of lung cancer surgery differs between the winter and the summer. The main reason for the better outcome is controversial; whether the results depending on more benefit from adjuvant treatment or better prognosis. This study showed the treatment effects of the vitamin levels which may result in vitamin replacement during cancer chemotherapy.^[6,11] Related to this study, high vitamin D levels proved to poten-

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tiate chemotherapy response to cisplatin gemcitabine in bladder cancer cell cultures.^[12] Also, in lung cancer, vitamin D receptor polymorphism is related to survival in both early and metastatic stage.^[11,13]

Potentially, there may be more than one mechanism for vitamin D and cancer growth, the action of spread and treatment response. In this study, we evaluated the correlation between the chemotherapy outcome and vitamin D replacement dose, and also, progression-free (PFS) and overall survival (OS) of the patients due to vitamin D replacement levels.

Methods

Study Participants

In the cross-sectional study, the archive records of patients diagnosing lung cancer at the Afyon Kocatepe University Oncology Department were retrospectively analyzed between 2012 and 2018. The patients who have vitamin D levels in 6 months before lung cancer diagnosis were included in the study. Also, the prescriptions in the hospital management system were investigated and the vitamin D replacements and doses recorded. The vitamin levels low-

er than 30 nmol/l is determined insufficient. The patients who have 300.000 IU or more were considered to have an adequate replacement. The patient characteristics, pathologic subtype, stage of the disease, treatment modalities, chemotherapeutic agents, chemotherapy outcome after the second or third cycle of chemotherapy were recorded. Also, patients who have EGFR, ALK or ROS-1 mutations were defined. The patients PFS and OS were calculated. The exclusion criteria's were lack of adequate cancer diagnosis, platinum-based first-line chemotherapy, and follow-up.

Ethics

The study was approved by the institutional board of Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations.

Statistical Analysis

The statistical analysis of the study performed with SPSS software (Statistical Package for The Social Sciences, version 22.0, SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether data conformed to a normal distribution. Descriptive data are presented as ei-

Table 1. The patient characteristics among the vitamin D replacement levels

Replacement levels	<300.000 IU		>300.000		p
	Male	Female	Male	Female	
Age	65.9	65.1	66.6	69.4	=0.48
Gender	192	23	27	5	=0.41
Vitamin D levels	13.53*		8.55*		=0.007
Genetic alteration	Positive	Negative	Positive	Negative	
	16	199	1	16	=0.7
Type of cancer	Adenocarcinoma	67	Adenocarcinoma	14	=0.69
	Squamous	92	Squamous	12	
	Small-cell	46	Small-cell	5	
	Large-cell	1	Large-cell	0	
	Undifferentiated	9	Undifferentiated	1	
Treatment	Cht	Cht+Rt	Cht	Cht+Rt	
	196	19	25	7	=0.07
Platinum agent	Cisplatin	Carboplatin	Cisplatin	Carboplatin	
	152	63	23	9	=0.89
Stage	3	4	3	4	
	95	120	12	20	=0.47
Response	Not responsive	Responsive	Not responsive	Responsive	
	37	178	3	29	=0.23
Cht response	Progressive	37	Progressive	3	=0.63
	Stabile	27	Stabile	4	
	Partial	148	Partial	24	
	Complete	3	Complete	1	

Cht: Chemotherapy; Rt: Radiotherapy; *: Median values.

ther means or median for continuous variables, frequencies and percentages are reported for categorical variables. Pearson X2 test is used to assessing the associations in categorical variables. OS and PFS curves are estimated by the Kaplan-Meier product-limit method.

Results

Two hundred forty-seven patients enrolled in the study. The patients divided into two groups depending on vitamin D replacement levels. There were 215 and 32 patients

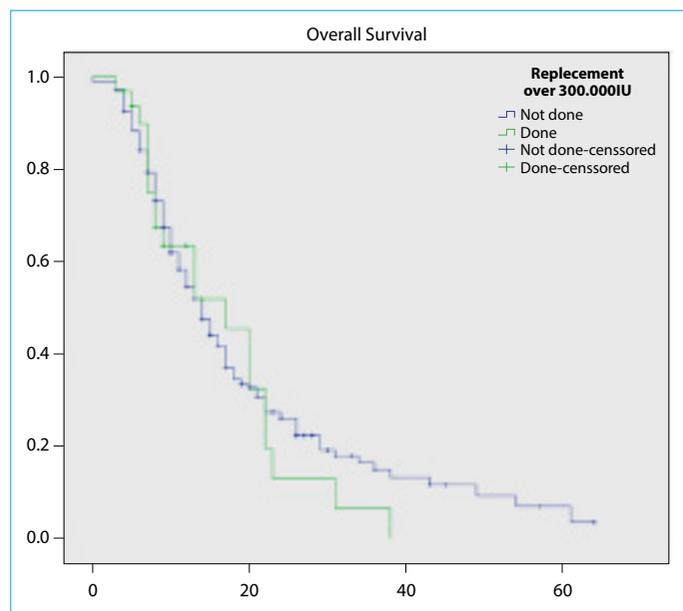


Figure 1. The OS of the patients when categorized among vitamin D replacement levels.

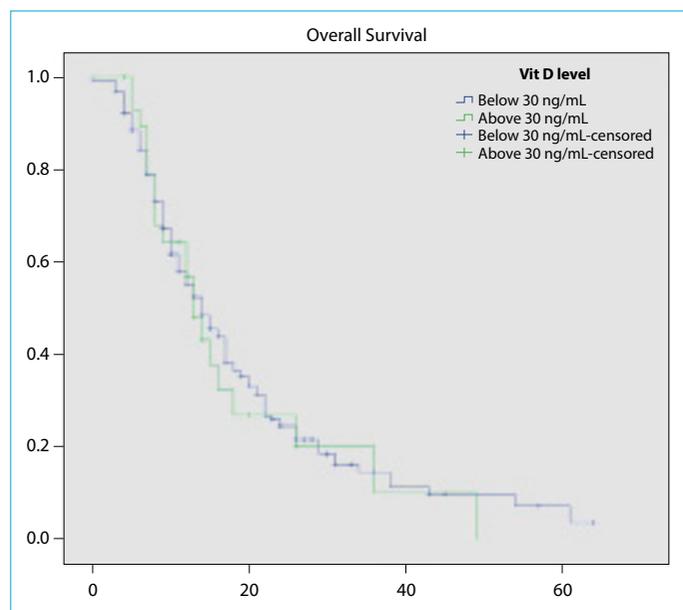


Figure 2. The OS of the patients when categorized among the vitamin D levels at the time of diagnosis.

who had vitamin D replacement less than 300.000 IU, and more than 300.000 IU respectively. The patients' characteristics are shown in Table 1. The mean age between groups was 65.8 and 67 respectively ($p=0.48$). The median vitamin D levels at the time diagnosis between replacement groups were significantly different. The median levels were 13.5 and 8.5 respectively ($p=0.007$). Types of cancers, genetic alterations, treatment modalities, platinum agents, stages, chemotherapy responses were similar among the groups.

There were no significant OS and PFS difference between groups due to the vitamin D replacement level (Fig. 1). Also, there was no difference in OS and PFS among the histologic subgroups (adenocarcinoma, squamous cell carcinoma, and small cell lung cancer). The patients categorized due to their vitamin D levels before treatment which was determined insufficiency (<30 ng/mL) and deficiency (<15 ng/mL). The survival and progression analyses were not significantly different among these groups (Fig. 2).

Discussion

In this study, we investigated the relationship between vitamin D replacement levels and platinum-based chemotherapy outcomes. Also, the prognostic value of vitamin D before treatment was analyzed. Vitamin D replacement levels were not significantly associated with chemotherapy outcomes in our study.

Vitamin D is known to have anti-proliferative effects on multiple cancer types including lung cancer. The active metabolite of vitamin D is considered to be responsible for the anti-cancer effect.^[14] Also, the variations in the vitamin D receptors are proven to be associated with platinum-based chemotherapy outcome in non-small cell lung cancer.^[15] These variations have a potential role in both risk and prognosis in human cancers.^[16] The vitamin D receptor polymorphisms have a prognostic effect on lung cancer; the mechanism is still unclear. The possible mechanisms are increased treatment response, decreased tumor growth and loss of metastatic capacity.^[4]

In a Japanese study, Akiba et al.^[17] reported daily supplement of 1200 IU of vitamin D for 12 months did not improve the relapse-free survival (RFS) or OS in squamous cell carcinoma and large cell carcinoma. This study was containing both early and advanced stage patients. Different from this study, our study was including only advanced or locally advanced patients. Also, our study included the four histologic types (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma). In a different study, Ma et al.^[18] found an association with low vitamin D levels and OS. The patients who have higher than 10 ng/mL have better survival, but PFS was not significant among

these groups. Also, when the patients split into two groups lower and higher than 20 ng/mL; the OS and PFS were not significant. By these results, we found no relationship between the insufficiency and deficiency of vitamin D and OS and PFS. These results may be directive to extremely low levels of vitamin D have a role in OS or PFS.

In previous cohort studies, the high levels of vitamin D early stages of lung carcinoma except squamous cell type tended to correlate with OS. Advanced stages of lung cancer did not have a significant correlation with OS when vitamin D considered.^[6,11,19,20]

In our current knowledge, this is the first human study which investigates the relationship between the vitamin D replacement levels and platinum-based chemotherapy outcome in four histologic subtypes of lung cancer. Future studies, which investigate both vitamin D and receptor polymorphism, maybe elucidative in this topic.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – I.B.; Design – M.A.; Supervision – M.U.; Materials – I.B., D.B.; Data collection &/or processing – I.B., D.B., H.D.; Analysis and/or interpretation – I.B., D.B.; Literature search – I.B., D.B.; Writing – I.B., D.B.; Critical review – M.A.

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