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Evaluation of Vitamin D level and Fatigue in Acute Leukemia Patients Undergoing Chemotherapy

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Abstract

The aim of this study is to evaluate vitamin D level and fatigue in acute leukemia patients undergoing chemotherapy. Forty one patients with acute leukemia (AL) undergoing chemotherapy were enrolled and 30 patients were prospectively examined the relationship between 25(OH) vitamin D and fatigue. Vitamin D levels were measured and patients with subnormal (< 32 ng/ml) were supplemented with 25(OH) vitamin D. Spearman Correlation Coefficients and Wilcoxon rank sum test were used for the comparison. Vitamin D deficiency and insufficiency in AL patients are similar to the general population. There was no significant correlation ($P > 0.05$) between vitamin D level and fatigue in the study. Therefore, Vitamin D supplementation may no help to improve fatigue in acute leukemia patients undergoing chemotherapy with vitamin D deficiency. However, Larger samples should be further examined the effect of vitamin D supplementation on fatigue in cancer patients with vitamin D deficiency.

Keywords: Vitamin D; Fatigue; Acute leukemia; Chemotherapy

Introduction

The relationship between vitamin D deficiency and chronic illnesses including cancer has been an emerging field of research [1,2]. There were reports that insufficient vitamin D levels in chronic lymphocytic leukemia patients linked to cancer progression and death [3] and low 25(OH) vitamin D3 levels were associated with adverse outcome in newly diagnosed, intensively treated adult acute myeloid leukemia [4]. Vitamin D Supplement comes in two forms: vitamin D3 (cholecalciferol), which is produced from the conversion of 7-dehydrocholesterol in human skin in response to sun exposure, and vitamin D2 (ergocalciferol), which is derived from fungal sources by activating ergosterol with ultraviolet light. Vitamin D2 is not naturally present in the human body and may have different actions within the body compared to those of vitamin D3. The active form of vitamin D is 1, 25(OH) 2D. It is obtained primarily through exposure of the skin to ultraviolet radiation in sunlight, but it can also be obtained from some foods and dietary supplements such as oily fish, fortified milk or orange juice, and vitamin D supplements [5]. Vitamin D is essential for the formation, growth, and repair of bones, normal calcium absorption and immune function [6].

Fatigue is the most distressing symptom experienced by cancer patients undergoing chemotherapy and its progression etiology is unknown [7]. The National Comprehensive Cancer Network (NCCN) defines cancer related fatigue as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive, or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[8]. Fatigue can significantly affect a patient's quality of life, leading to poor compliance with further treatment and may result in a failure to complete potentially curative treatment [9, 10]. Failure to complete treatment can result in many consequences including emotional distress and disease progression.

Some studies suggest that serum 25-hydroxyvitamin D [25(OH) D] levels below 30 ng/ml are associated with pain and chronic fatigue [11]. However, a cross-sectional study conducted by Stockton et al. revealed that fatigue was related to physical function but not vitamin D status in the systemic lupus erythematosus patients with vitamin D repletion [12]. It is still unclear whether normal 25 (OH) D levels (32 ng/ml) are associated with improved cancer/chemotherapy related fatigue [13]. We therefore conducted a prospective pilot study to prospectively examine the relationship between serum levels of 25(OH) D and fatigue levels for acute leukemia (AL) patients undergoing chemotherapy with the hypothesis that patients with normal 25(OH) vitamin D3 level will have less fatigue and an improved quality of life.

Subjects and Methods

Patients

The samples consisted of adult patients who were admitted to Roswell Park Cancer Institute (a National Cancer Institute Comprehensive Cancer Center) Leukemia Service in Buffalo, New York. The patients were enrolled between September, 2012 and March, 2013. Inclusion criteria were age 18 years or older, newly diagnosed AL confirmed by pathology, lack of previous history of any other type of cancer excluding skin cancer, no prior chemotherapy, able to read and write in English, able to independently complete the fatigue scale

questionnaires without the help of others , participants must have understood the investigational nature of the study and signed an Institutional Review Board (IRB, an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects) approved, written, informed consent. Exclusion criteria were a diagnosis of psychiatric disorder, chronic fatigue syndrome, pregnant or nursing, a history of hypercalcaemia or kidney stones.

Data collection

Collection of clinical data was achieved by using the electronic medical record (EMR). Serum 25(OH)D levels were measured at the time of AL diagnosis and for a maximum of two months. These measurements were performed as standard of care. Patients filled out the Brief Fatigue Inventory (BFI, adopted from the University of Texas M. D. Anderson Cancer center with permission) pre-treatment and monthly thereafter for a maximum of two months [14]. The BFI has been validated as a short and comprehensive instrument to assess the severity of fatigue and the impact of fatigue on daily functioning [quality of life (QOL)] in both clinical screening and research studies. QOL assessment was part of BFI and it consists of six items including general activity, mood, walking ability, normal work, relations with other people and enjoyment of life with each item scoring from 0-10. It may be completed by a patient in five minutes.

Vitamin D supplementation

Patients were divided into two vitamin D groups (Normal: ≥ 32 ng/ml and Subnormal: < 32ng/ml) according to their baseline serum 25(OH) vitamin D3 level. Patients in the subnormal vitamin D group were provided with Vitamin D supplements (ergocalciferol) during chemotherapy based on 25(OH) vitamin D3 level according to the Leukemia Service treatment algorithm. Supplementation was provided as standard of care with commercially available 25(OH) vitamin D3. For the patients with vitamin D levels < 20 ng/ml, 50,000 units of vitamin D2 or D3 was given once weekly for 8 weeks, then 800 to 1000 units daily thereafter for maintenance. For the patients with vitamin D levels 20-30 ng/ml, 800 to 1000 units of vitamin D2 or D3 was given daily for maintenance only. The first month of treatment was inpatient, thus supplementation was controlled by hospital staff. After discharge, compliance was assessed by a study calendar/diary. The study was approved by the IRB and conducted according to the Declaration of Helnsiki.

Statistical analysis

Descriptive statistics such as frequencies and relative frequencies were computed for all categorical variables. Numeric variables were summarized using simple descriptive statistics such as the mean, standard deviation, median, range, etc. The Spearman Correlation Coefficients were used to test the association between serum of 25(OH) vitamin D3 levels, fatigue score and QOL at each time point. The Wilcoxon rank sum test was used to compare the groups (25(OH)D < 20 ng/ml versus ≥ 20 ng/ml), in regards to fatigue score and QOL. A significance level of 0.05 was used for each hypothesis test and p-value ≤ 0.05 was considered as significance. Data analyses were performed using SAS, version 9.3, statistical software (SAS Institute., Cary, NC).

Results

We enrolled 41 patients in the study, but nine patients died during the first cycle of chemotherapy, and two patients were lost to follow up. Therefore only 30 patients were accounted for data analysis. There were only two patients (7%) with normal vitamin D level (≥ 32 ng/ml) and 28 patients (93%) with vitamin D insufficiency. There were six patients started at the 3rd cycle of chemotherapy and the sample size was too small for data analysis so those patients were not included. The demographic and clinical characteristics of the study participants are presented in Tables 1 and 2. A total of 30 patients were enrolled in the study with a mean age of 60.5 ± 15 years. There were 21 (70%) males and nine (30%) females with 27 (90%) caucasians.

Variable	Statistic	VITD1 < 20	VITD1 ≥ 20	Overall
AGE	Mean (SD)/N	61.6 (16.3)/12	59.7 (14.5)/18	60.5 (15)/30
	Median (Range)	65.5 (24,80)	64.5 (24,79)	65.5 (24,80)
BFI1	Mean (SD)/N	16.8 (8.8)/12	15.6 (7) / 18	16.1 (7.6)/30
	Median (Range)	17.5 (3, 28)	16.5 (1, 26)	17 (1, 28)
QOL1	Mean (SD)/N	22.8 (14)/12	26.4 (13.4)/18	25 (13.5)/30
	Median (Range)	26 (3, 45)	27.5 (2, 44)	25 (2, 45)
VITD: 25(OH) vitamin D3; BFI: Brief Fatigue Inventory fatigue severity; QOL: the impact of fatigue on daily functioning				
* VITD1, BFI1, QOL1: Baseline 25(OH) vitamin D3 level, fatigue severity score, quality of life score;				

Table 1: Patients baseline characteristics (n = 30).

The Scatterplot for 25(OH) vitamin D3 level versus fatigue level, and versus QOL scores from the base line and after the first cycle of chemotherapy showed very weak association (Figure 1, each scatter presents a patient, with two different vitamin levels: D1 and D2). Spearman Correlation Coefficients test revealed no significant correlation between 25(OH) vitamin D3 and fatigue level or QOL scores at baseline (0.07876, P-values 0.6791 and 0.09502, P-values 0.6175, respectively) and following the first cycle of chemotherapy (0.07139, P-values 0.7522 and 0.13129, P-values 0.5603, respectively; Table 3).

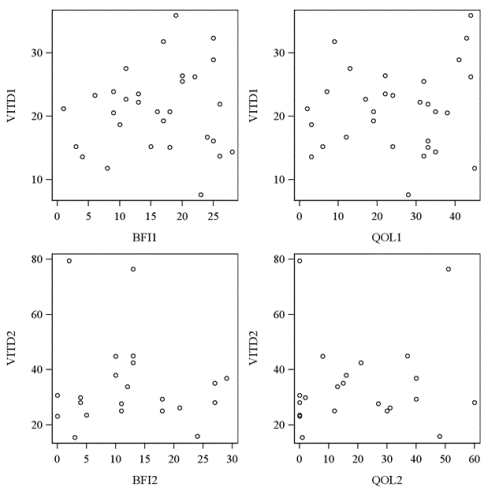

Figure 1: Scatterplot of correlation between VITD level and BFI/QOL score.

Then, the cohorts were divided into groups based on 25(OH) vitamin D3 levels: < 20 ng/ml, and 20 ng/ml. Wilcoxan rank-sum tests showed no significant difference between the two 25(OH) vitamin D3 groups (P-value > 0.05; Table 4).

There were 11 patients with 25(OH) vitamin D3 < 20 ng/ml at baseline who received 50.000 international units of Vitamin D supplements. At the time prior to start second cycle of chemotherapy, eight of the eleven patients' 25(OH) vitamin D3 levels were above normal [25(OH) vitamin D3 32 ng/ml]; only three of them were still insufficient [25(OH) vitamin D3 < 32 ng/ml, but 20 ng/ml], but increased to near normal (close to 30 ng/ml). Of interest, two patients whose 25(OH) vitamin D3 levels were above normal at diagnosis had insufficient 25(OH) vitamin D3 at the beginning of the second cycle.

Variable	Level	VITD1 < 20	VITD1 ≥ 20	Overall
GENDER	Female	3 (25%)	6 (33.3%)	9 (30%)
	Male	9 (75%)	12 (66.7%)	21 (70%)
RACE	Other	0 (0%)	3 (16.7%)	3 (10%)
	White	12 (100%)	15 (83.3%)	27 (90%)
KPS	<70	3 (25%)	2 (11.1%)	5 (16.7%)
	≥70	9 (75%)	16 (88.9%)	25 (83.3%)
DX	AML	11 (91.7%)	16 (88.9%)	27 (90%)
	ALL	1 (8.3%)	2 (11.1%)	3 (10%)
KPS: Karnofsky Performance Status at AL diagnosis. DX: diagnosis. AML: Acute Myeloid Leukemia. ALL: acute lymphoid leukemia.				

Table 2: Patients baseline characteristics (n = 30).

Discussion

Fatigue is the most distressing side effect of the cancer patients underwent chemotherapy. The management of fatigue in cancer patients is one of the important and challenging issues. The 93% (28 out of 30) of patient with vitamin D insufficiency (25(OH) vitamin D3 < 32 ng/ml) in this study with AL patients was similar to that of report from hematology-oncology clinic [13]. Vitamin D insufficiency was highly prevalent among advanced cancer patients with fatigue [15]. There was a report that vitamin D supplementation significantly increased 25(OH) vitamin D3 levels and reduced joint pain and fatigue in breast cancer patients [16]. There are many factors affecting 25(OH) vitamin D3 levels, which include UVB exposure, latitude, race, age, and obesity [17]. Cancer and chemotherapy related fatigue occurs with other signs and symptoms, such as anemia, pain, in symptom clusters [9]. A study by Koczwara et al demonstrated that chemotherapy is associated with a fall in serum 25(OH) vitamin D3 [18]. Zick et al. found that increased consumption of whole grains, vegetables, and foods rich in certain anti-inflammatory nutrients was associated with decreased level of fatigue [19]. High vitamin D foods are also rich in anti-inflammatory nutrients, therefore the nutrition status of the patients and dietary consumption are other factors to be considered 25(OH) vitamin D3 levels and cancer/chemotherapy related fatigue.

Variable	Correlation Coefficients	P-value
VITD1 vs BFI1	0.07876	0.6791
VITD1 vs QOL1	0.09502	0.6175
VITD2 vs BFI2	0.07139	0.7522
VITD2 vs QOL2	0.13129	0.5603
VITD2, BFI2, QOL2: Vitamin D level, fatigue severity score, quality of life score after first cycle of chemotherapy		
Note: Statistical analysis was done using Spearman Correlation Coefficients. P-value > 0.05 indicated that no significant correlation was found.		

Table 3: Correction between VITD and BFI/QOL in patients (n = 30).

We comprehensively reviewed the literature in the terms of "vitamin D" and "Cancer/Chemotherapy related symptoms" using PubMed, MEDLINE, CINAHL with full text, and SCOPUS in the last five years. Each study was appraised individually for its purpose, sample size, design, data collection and analysis, findings, and conclusions. The systematic literature review indicated that the evidence of vitamin D improvement of cancer/chemotherapy related fatigue was sparse and inconclusive [1,12,15,16,20-24].

The current study is the first pilot study to examine the relationship between vitamin D and cancer/chemotherapy related fatigue in AL patients. There are several limitations to this study that include small sample size, lack of a comparison group; brief follow up period; lack of other variables such as infection, chemotherapy regimen, hemoglobin, and TSH at the time of survey. The initial planned sample size calculations were based on two tailed t-test at each time point. At 0.05 level of test, total number of 50 subjects of at least 80% can be obtained if the difference in the true mean of fatigue score is at least 0.85 standard deviations. The authors would like to perform a retro perspective study by use same sample, but add other variables such as performance status, comorbidities, chemotherapy regimen, hemoglobin, white blood cell count, platelet count, TSH and albumin in addition to 25(OH) vitamin D3 level.

Variable	Statistic	VITD1 < 20	VITD1 ≥ 20	Overall	P-value
BFI1	Mean (SD)/N	16.8 (8.8)/12	15.6 (7)/18	16.1 (7.6)/30	0.702
	Median (Range)	17.5 (3, 28)	16.5 (1, 26)	17 (1, 28)	
QOL1	Mean (SD)/N	22.8 (14)/12	26.4 (13.4)/18	25 (13.5)/30	0.5448
	Median (Range)	26 (3, 45)	27.5 (2, 44)	25 (2, 45)	
BFI2	Mean (SD)/N	13.5 (9.1)/11	11.5 (9.2)/11	12.5 (9)/22	0.6121
	Median (Range)	13 (0, 29)	11 (0, 27)	11.5 (0, 29)	
QOL2	Mean (SD)/N	22.4 (16.6)/11	18.7 (22.1)/11	20.5 (19.1)/22	0.5293
	Median (Range)	24.5 (1, 48)	15 (0, 60)	15 (0, 60)	
Note: Statistical analysis was done using exact Wilcoxon rank-sum test. P-value > 0.05 indicated that no significant difference between vitamin D groups.					

Table 4: Statistical analysis of the differences between vitamin groups.

The question of whether vitamin D would improves cancer/ chemotherapy related fatigue is worthy of further exploration in cancer patients. In our study, Spearman Correlation Coefficients test revealed no significant correlation between vitamin D level and fatigue or QOL scores at the baseline and following the first cycle of chemotherapy (Table 3).The result need to be validated with larger population samples. Future studies could examine the relationship between vitamin D levels and cancer/chemotherapy related fatigue in cancer patients with larger samples size of participants from various age, ethnic backgrounds, different geographic areas, with various rtypes and stages of cancer and different chemotherapy regimens. If cancer/ chemotherapy related fatigue is due to low levels of vitamin D, then future studies also need to include randomized controlled trials to determine the optimal dosing of vitamin D to minimize these symptoms. The comparison should evaluate the fatigue scores of cancer patients with Vitamin D deficiencies who have received Vitamin D supplementation vs. cancer patients with Vitamin D deficiencies who have not received Vitamin D supplementation.

The medical community has recently begun to acknowledge the importance of vitamin D deficiency for a variety of clinical applications including cancer prevention and treatment. Vitamin D deficiency is very common in the United States. A continually growing number of clinicians are checking 25(OH) vitamin D3 levels as their routine practice. Vitamin D supplements are economical and easily to be administered and well tolerated by patients. With the awareness of the role of 25(OH) vitamin D3, hopefully there will be more research on vitamin D and cancer/ chemotherapy related fatigue.

In conclusion, we found that Vitamin D deficiency and insufficiency in AL patients are similar to the general population. There was no significant correlation ($P > 0.05$) between vitamin D level and fatigue. Vitamin D supplementation may not improve fatigue and quality of life in AL patients undergoing chemotherapy with vitamin D deficiency. However, we have insufficient data with limited enrolled patients to support the results. Therefore, further studies are required to validate our findings.

Conflict of interest

The authors report no conflict of interests.

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