Support Care Cancer (2016) 24:3105–3110
DOI 10.1007/s00520-016-3126-1

ORIGINAL ARTICLE

Low serum vitamin D occurs commonly among multiple myeloma patients treated with bortezomib and/or thalidomide and is associated with severe neuropathy

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Received: 23 November 2015 / Accepted: 9 February 2016 / Published online: 23 February 2016

Abstract
Purpose Previous studies have shown that low serum vitamin D levels have been associated with many skeletal and non-skeletal disorders. We studied the relationship between 25-hydroxyvitamin D (25D) levels and motor and sensory peripheral neuropathy (PN) among multiple myeloma (MM) patients who have been treated with bortezomib and/or thalidomide.
Methods We performed a study of 111 MM patients who had received at least one of these two agents for at least 12 weeks by correlating physical exam/neurologic assessment findings with patient self-assessment responses.
Results The median age of study patients was 66 years (range 42–89 years) and 54 % were males. 25D levels were determined, and complete history and physical and neurologic examinations were performed at the same study visit. In addition, study subjects completed questionnaires regarding symptoms related to motor and sensory PN. Overall, patients had a median serum 25D level of only 32 ng/ml; 42 % of patients were considered either 25D-deficient (<20.0 ng/mL; 16 % of patients) or 25D-insufficient (20.0–29.9 ng/mL; 26 %). Notably, we found that 25D-deficient MM patients were more likely to have severe PN (>grade 2) of both motor ($p = 0.0415$) and sensory ($p = 0.0086$) types although the overall incidence of PN was not higher in this patient population.
Conclusion These results show that the severity of peripheral neuropathy is associated with lower vitamin D levels and provides the rationale for monitoring vitamin D for myeloma patients especially those receiving drugs associated with the development of peripheral neuropathy.

Keywords Multiple myeloma · Bortezomib · Thalidomide · Peripheral neuropathy · Vitamin D

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Introduction

Vitamin D has been found over the past few decades to play a major role in many disease processes. Based on a 2005–2006 National Health and Nutrition Examination (NHNE) survey, 42 % of adults in the USA were vitamin D deficient [1]. Vitamin D deficiency is well-documented as being associated with osteoporosis and skeletal-related events (SREs), and some studies have shown that adequately correcting this deficiency has been shown to decrease the risk of fractures [2, 3]. However, other studies have found that supplementation with both vitamin D and calcium, rather than vitamin D supplementation alone, reduced the risk of fracture in some populations [4–6]. Low serum vitamin D levels have also been associated with increased mortality [7, 8]. In addition, lower levels of vitamin D have been linked with obesity, diet and activity level as well as various malignancies [2, 9–12], and have also been associated with many forms of psychiatric illness [13]. Vitamin D deficiency in asthmatics has been linked to a 25 %

greater risk of asthma exacerbations [14]. In early pregnancy, low vitamin D has been associated with an increased risk of preterm birth [15]. Some studies have also shown that low levels are associated with neurologic disorders including an increased risk of developing Alzheimer's disease and dementia [16] as well as multiple sclerosis [17]. Other studies have shown vitamin D deficiency to be associated with muscle weakness and loss of muscle mass [18].

Peripheral neuropathy (PN) is a well-documented side effect of many medications and is a prominent symptom of several chronic diseases. For instance, statins [19] for hyperlipidemia and isoniazid [20] for tuberculosis treatment/prophylaxis have been known to cause PN. PN is also a symptom of long-standing diabetes [21]. Other risk factors for PN include trauma, alcohol abuse, viral infections, exposure to toxins, autoimmune diseases, as well as various nutrient deficiencies such as vitamin B, alpha-lipoic acid, and folic acid [22]. With regards to multiple myeloma (MM), medications such as bortezomib [23, 24], thalidomide [20, 23, 25], pomalidomide [25], and vincristine [25] have been shown to be associated with the development of PN, while MM itself has also been reported to cause PN [23]. Known risk factors for developing PN while on bortezomib or thalidomide include higher doses of these drugs [26], diabetes mellitus [27], and baseline PN [27]. There was also found to be a genetic component to PN, as 56 SNPs have been found to be associated with bortezomib-induced PN in one study [28]. Bortezomib is also known to inhibit the degradation of the vitamin D receptor, causing elevated levels of this receptor [29]. Elevated levels of the receptor results in vitamin D sequestration and decreased serum vitamin D levels [29].

The objective of this study is to determine the relationship between the incidence and severity of myeloma treatment-induced PN and serum 25-hydroxyvitamin D (25D) levels among MM patients previously treated with at least 12 weeks of therapeutic dosing of bortezomib and/or thalidomide. To accomplish these objectives, data was collected from multiple sources containing investigator assessments including a current history, physical and detailed neurologic examination, chart review, and patient self-reported assessments.

Materials and methods

Patient population

The inclusion criteria were adult patients (18 years of age or older) with MM diagnosis based on the standard criteria (Durie 1986) [30], who have completed at least 12 consecutive weeks of treatment prior to the study enrollment. The treatment regimens included bortezomib (≥1.0 mg/m^2 dosed at least three times per 4-week period) and/or thalidomide (≥50 mg daily). Exclusion criteria were patients with POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein), and skin changes), plasma cell leukemia, and primary amyloidosis. Individuals with a serious medical or psychiatric illness or any condition or abnormality that would prevent the subject from signing the informed consent form and thus interfere with the participation in this study were also omitted. Written informed consent was obtained from all patients before they entered the study, and all procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study design

This was a non-randomized, multi-center study. A total of 111 patients were enrolled in the study. Each patient underwent a history and physical exam which also included a neurologic assessment by the participating hematologist/oncologist. The neurologic assessment included testing of sensory and motor components as well as gait and deep tendon reflexes, with specific attention to the severity of PN assessed with patient history and physical exam and graded based on the NCI Common Toxicity Criteria for Adverse Events (CTCAE) scale. Each patient also had peripheral blood samples collected for vitamin D levels (25D), complete blood counts, and metabolic panel, all of which were analyzed at each site's respective lab. Vitamin D was measured either with liquid chromatography-tandem mass spectrometry (LCMS/MS) or immunoassay depending on the site and time of draw. LCMS/MS and the immunoassay have been shown to be comparable methods of measuring vitamin D [31]. Each patient completed self-assessment surveys including the Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTx-13) Questionnaire and the short-form McGill Pain Questionnaire (SF-MPQ).

All assessments and testing were completed within 2 weeks of consent to the study. Any patient who consented to this clinical trial but could not complete study requirements within the 2-week window were re-consented and re-assessed to ensure consistency throughout the study.

Statistical analysis

Descriptive statistics were used to analyze demographical and clinical sample data. Unpaired *t* tests were used to analyze correlation between vitamin D levels and incidence and severity of PN. Since laboratory data came from several different study locations prior to its analysis, all data was converted to the standard units for each item measured, as needed. All

analyses were conducted using GraphPad Prism 4 for Windows. p value was set at <0.05 for statistical significance.

Results

A total of 111 patients were screened and enrolled in the study. Among all enrolled patients, two patients were excluded from assessments for the following reasons: missing follow-up information (n = 1) and voluntary withdrawal from the study (n = 1). Patients were enrolled at study centers in six different sites across the USA. Patient characteristics are summarized in Table 1. Fifty-nine (54 %) patients were males, and the median age of the patients in the study was 66 years (range, 42–89 years). Eighty-one percent of patients identified as Caucasian, 8 % identified as African-American/Black, 5 % identified as Hispanic or Latino, 3 % identified as Asian, 1 % identified as Native Hawaiian/Pacific Islander, and 3 % identified as Other. The median serum 25D level in our study sample was 32.0 ng/ml (range, 11.4–85.5 ng/ml). Forty-two percent of patients were either 25D-deficient (<20.0 ng/ml; 16 %) or 25D-insufficient (20.0–29.9 ng/ml; 26 %). Fifty-nine percent of patients experienced some degree of PN, with a median motor PN (mPN) score of 1 and median sensory PN (sPN) score of 1. Eleven (10 %) of patients had a past history of diabetes mellitus.

Table 1 Study patient characteristics

Characteristic	Number of patients (N = 109)	Percentage (%)
Age, years		
- Median	66	
- Range	42–89	
Gender		
- Male	59	54
- Female	40	46
Ethnicity		
- Caucasian	88	81
- African-American/Black	9	8
- Hispanic	5	5
- Asian	3	3
- Native Hawaiian/Pacific Islander	1	1
- Other	3	3
Vitamin 25D		
- Median (ng/ml)	32.0	
- Deficient (< 20.0 ng/ml)	17	16
- Insufficient (20.0 –29.9 ng/ml)	29	26
History of Vitamin D supplementation (current and/or past)	43	39
Diabetes mellitus	11	10

The analyses of this study are summarized in Table 2. In comparing 25D with PN, there was no relationship between the level of 25D (deficiency or insufficiency) and occurrence of either mPN (p = 0.7982, p = 0.3826) or sPN (p = 0.7982, p = 0.1834). However, the severity of PN (>grade 2) was worse among patients with 25D deficiency for both mPN (p = 0.0415) and sPN (p = 0.0086). Additionally, patients with 25D insufficiency also had more severe sPN (p = 0.0478), and borderline significance was found with respect to the severity of mPN (p = 0.0573). There was also borderline statistically significant differences found between 25D deficiency or insufficiency and higher FACT/GOG-NTx-13 scores (p = 0.0808, p = 0.0543, respectively).

In relation to pain levels, no significant difference was found between 25D deficiency or insufficiency and the following markers from the SF-MPQ: pain description total score (p = 0.0754, p = 0.1360), pain intensity line fraction (p = 0.3128, p = 0.4236), and present pain score (p = 0.5290, p = 0.1972).

Discussion

The findings of this study show that low vitamin D levels occur commonly among MM patients who have been treated with bortezomib or thalidomide but are actually quite similar to those found in other studies of the adult population in general [1]. Notably, the severity of PN experienced by these patients is associated with lower serum levels of 25D. Specifically, vitamin D deficiency is associated with more severe forms of both sPN and mPN in these patients.

Higher incidence of vitamin D deficiency among MM patients as compared to the general population has been previously reported [32]. This phenomenon was found to be independent of gender, age, and severity of the disease, but possibly linked to the reduced activity levels of MM patients resulting in the decreased exposure to sunlight [32]. Also of note, patients treated with long-term glucocorticoid therapy are also at risk for vitamin D deficiency [18]. It has also been proposed that vitamin D deficiency correlates with higher serum CRP, creatinine, and ISS staging, indicating that this deficiency may lead to worse outcomes for MM patients [33]. Vitamin D deficiency has also been linked to other cancer types. For instance, inverse relationships between 25D levels and the risks of colorectal and breast cancer have been identified [18, 34, 35]. Interestingly, prostate cancer risk was reported to have a positive association with 25D levels, where men with lower vitamin D concentrations had significantly decreased risk of prostate cancer and vice versa [36]. In some cancer patients, higher vitamin D levels at the time of diagnosis or treatment have also been found to be associated with improved survival [18]. In a 2006 study of 256 advanced MM patients treated with bortezomib, 35 % of patients developed

Table 2 Vitamin D deficiency and insufficiency analysis results

Characteristic/Measure	25D < 20 ng/ml	25D ≥ 20 ng/ml	*p*-value	25D < 30 ng/ml	25D ≥ 30 ng/ml	*p*-value
Number of patients	17	92		46	63	
mPN						
- Incidence	10 (59 %)	51 (55 %)	0.7982	28 (61 %)	33 (52 %)	0.3826
- Median score	1	1	0.0415*	1	1	0.0573
sPN						
- Incidence	10 (59 %)	51 (55 %)	0.7982	30 (65 %)	33 (52 %)	0.1834
- Median score	1	1	0.0086*	1	1	0.0478*
FACT/GOG-NTx score (possible 0–52)						
- Median	8†	8†	0.0808	9†	7†	0.0543
- Range	2–45	0–30		0–45	0–30	
Pain description score (possible 0–45)						
- Median	5†	4†	0.0754	5†	5†	0.1360
- Range	0–43	0–25		0–43	0–25	
Pain intensity length percentage—median	15.3%†	15.5%†	0.3128	15.46%†	12.50%†	0.4236
Present pain score (possible 0–5)						
- Median	0†	0†	0.5290	1†	0†	0.1972
- Range	0–4	0–4		0–4	0–4	

*significant at $P < 0.05$

† excludes incomplete/invalid surveys

treatment-emergent PN, and 37 % of those with PN had high-grade (grade 3 and 4) treatment-emergent disease [37]. Of the patients with high-grade PN, 71 % had resolution or improvement of PN with dose reduction or medication discontinuation [37]. Other studies of bortezomib-induced PN have shown an incidence of 44–70 %, with grade 2 or higher PN in 19–40 % of patients [38]. Thalidomide-induced PN was identified in 30–55 % of patients, with grade 2 or higher PN in 17–24 % of patients [36]. Known risk factors for developing PN in MM patients on bortezomib and/or thalidomide regimens include treatment drug dosage, diabetes mellitus, and genetic predispositions [26–28, 39].

Prior studies have indicated a similar association between low serum vitamin D levels and the severity of peripheral neuropathy among diabetic patients [21, 40]. A study in 2008 showed that supplementation with vitamin D may result in lower PN pain scores for previously vitamin D-insufficient patients but that study was conducted in a non-randomized, non-blinded patient population [41]. In the current study, there was not a statistically significant difference between vitamin D insufficiency and pain scores. When correlating vitamin D levels with FACT/GOG-NTx13 scores, there was a trend toward differences when analyzed at either the vitamin D deficiency or insufficiency levels but further studies will need to be conducted to confirm this association.

There are several limitations to this study. Our study population had a large proportion of Caucasian patients, which may limit its external validity, especially since the NHNE Survey showed that African-Americans had the highest prevalence of vitamin D deficiency at 82 %, followed by Hispanics at 69 %, even though the national average was lower at 42 % [1]. However, a study from 2013 showed that African-Americans had lower total serum 25D levels, but no difference in the level of bioactive vitamin D levels due to lower serum levels of vitamin D-binding protein [42]. There is also response bias for some of the questionnaires. The SF-MPQ for some participants had incompletions in some or all parts of the survey thus making 4–8 % of the data unevaluable.

Despite several limitations, this is the first study demonstrating the relationship between vitamin D levels and severity of peripheral neuropathy among cancer patients. Previously, a case report published in 2011 described a MM patient undergoing bortezomib-based treatment who had developed worsening PN [43]. The patient was subsequently treated with 3000 IU of vitamin D daily and physiotherapy. After 4 months of this treatment, the patient had improvement of PN symptoms, even though his MM deteriorated. We also add an additional risk factor for developing PN among patients receiving bortezomib or thalidomide, drugs known to be associated with the development of PN. However, further studies are warranted to explore whether early detection and subsequent treatment of the vitamin D deficiency prior to initiation of MM therapy that includes vitamin D supplementation as concomitant medication will result in preventing the occurrence of severe neuropathy. It will also be important to determine whether supplementing patients who have or are currently receiving bortezomib and/or thalidomide may prevent the

development of severe neuropathy or reduce its severity. Lastly, it will be interesting to investigate if the relationship of low vitamin D levels to the severity of neuropathy also is observed among cancer patients receiving other neuropathic drugs such as taxanes [26]. Further studies should be performed to answer these questions.

Acknowledgments This study was sponsored by Millennium, the Takeda oncology company.

Compliance with ethical standards

Conflict of interest Dr. Treisman is a consultant for Prometheus Laboratories. Dr. Berenson is a consultant and receives honoraria and research funding from Takeda, Amgen, Jansen, Celgene, and Bristol-Meyers-Squibb. Ms. Swift receives honoraria from Celgene, Takeda-Millennium, Bristol-Meyers-Squibb, and Onyx-Amgen.

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