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Vitamin D Deficiency in Pediatric Hematopoietic Stem Cell Transplantation Patients Despite Both Standard and Aggressive Supplementation

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Abstract

We recently reported that more than 70% of pediatric and young adult patients had a vitamin D (VD) deficiency at the time of their hematopoietic stem cell transplantation (HSCT). Moreover, VD deficiency was associated with inferior survival at 100 days after transplantation. The goal of the present study was to evaluate the VD requirements needed to maintain an optimal VD level (30 to 60 ng/mL) during the first 3 months after transplantation using real-time VD monitoring and personalized VD supplementation. We examined 2 cohorts in this study: cohort 1, the "preintervention" cohort (n = 35), who were treated according to National Kidney Foundation guidelines for VD therapy, and cohort 2, the "intervention" cohort (n = 25) who were treated with high-dose VD with an aggressive dosage increase in those who remained VD-insufficient. Results from cohort 1 showed that despite aggressive monitoring and VD supplementation, therapeutic vitamin D levels were difficult to achieve and maintain in HSCT recipients during the early post-transplantation period. Only 43% of cohort 1 achieved a therapeutic VD level, leading to our intervention in cohort 2. Outcomes improved in cohort 2, but still only 64% of cohort 2 patients achieved a therapeutic VD level despite receiving >200 IU/kg/day of VD enterally. The median VD level in patients who did achieve sufficient levels was 40 ng/mL, with only 1 patient in each cohort achieving a supratherapeutic but nontoxic level. These data indicate that standard guidelines for VD replacement are inadequate in HSCT recipients, and further work is needed to define more appropriate dosing in this clinical setting.

Keywords

Vitamin D deficiency; 25-hydroxyvitamin D; Hematopoietic stem cell transplantation

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INTRODUCTION

We have previously reported a high frequency of vitamin D (VD) deficiency in a cohort of children undergoing hematopoietic stem cell transplantation (HSCT), mostly for nonmalignant diagnoses. Our data also showed an association between VD deficiency and reduced survival in this group of patients. Importantly, all children with sufficient VD before HSCT became VD-deficient in the first 100 days after transplantation, despite receiving current standard recommended vitamin supplementation via total parenteral nutrition (TPN) and vitamins present in food and enteral formulas. Children who were VD-deficient before HSCT generally remained deficient, despite supervision by a registered dietician prescribing currently recommended supplementation [1].

Currently, a 25-hydroxy VD [25(OH)D] level <20 ng/mL is considered indicative of VD deficiency, and a level between 20 and 29 ng/mL indicative of VD insufficiency. A VD 25(OH) D level in the range of 30 to 60 ng/mL is considered optimal [2]. In a healthy individual, maintenance of a serum level at least 30 ng/mL requires approximately 2200 to 3000 IU/day of VD from all sources, including ultraviolet light exposure, food intake, and dietary supplements [3–5]. The current Food and Drug Administration recommendation for a daily VD supplement of 400 to 600 IU of VD/day assumes that a person has a healthy lifestyle with adequate sun exposure and vitamin-rich nutrition. The recommended dose is not adjusted in any way for patient age or weight. Moreover, patients with acute and chronic illnesses often have very limited sun exposure and a poor diet, raising concern that these recommendations are inadequate for HSCT recipients [6,7].

Symptoms of VD deficiency can be nonspecific, especially in a HSCT patient population, including fatigue, altered mood and depression, insomnia, skin and hair changes, muscle weakness, headache, and many symptoms may be attributed to the transplantation process and overlooked. In addition, there are no common practices for monitoring VD status in patients undergoing HSCT and no guidelines for VD supplementation or treatment in this population [8].

Our initial data suggested that much higher doses of VD supplements are needed for HSCT recipients than those currently recommended for supplementation and therapy in the general population with VD deficiency. Based on this observation, we initiated personalized VD dosing, adjusted to a moderate extent for weight, during the early post-transplantation period. Our goal in this study was to establish the VD requirements needed to achieve and maintain sufficient VD levels during the first month after HSCT, when vitamin and nutrient metabolism may be especially impaired.

METHODS

All patients scheduled to undergo HSCT at Cincinnati Children’s Hospital Medical Center between April 1, 2015, and December 31, 2015, received prospective VD monitoring and supplementation. VD levels and dose adjustments were documented in the medical record in real time. Institutional Review Board approval was obtained to review medical data. Serum 25(OH) D levels (VD) were measured in a Clinical Laboratory Improvement Amendments–

certified clinical laboratory at our institution before the start of HSCT (baseline level), and monthly thereafter. A VD level ≥30 ng/mL was defined as sufficient based on Pediatric Endocrine Society recommendations [9]. Therapy was initiated before initiation of the preparative regimen, with the goal of maintaining VD at an optimal level of 30 to 60 ng/mL.

Two consecutive cohorts of patients were examined in this study. Cohort 1 (the preintervention cohort) included consecutive HSCT recipients who underwent prospective VD monitoring and received VD supplementation or therapy based on National Kidney Foundation Guidelines, as listed in Table 1. The recommended dose was doubled in those patients who remained VD-insufficient.

Cohort 2 (the intervention cohort) received prospective VD monitoring and uniform clinical interventions based on VD supplementation and therapy guidelines for HSCT recipients that were derived from cohort 1 data examining VD requirements during the first 30 days after HSCT. This dosing strategy used 4 different initial starting doses according to weight categories, as shown in Table 2.

Enteral VD doses and VD administered in TPN were recorded. Currently, a VD dose of 400 IU/day is prescribed in TPN as a standard vitamin supplementation for all patients weighing >3 kg. By convention, the recommended dose of VD supplementation in TPN has not been adjusted for weight, with the same supplemental dose recommended for a 4-kg infant and a 100-kg adolescent. For comparison of recommended and actual dosing, we converted all doses into IU/kg/day.

For statistical data analysis, continuous and categorical variables were summarized using median (range) and frequency (percentage), respectively.

RESULTS

Seventy-five patients underwent HSCT during the 9-month study period. Fifty patients underwent HSCT during the “preintervention” study period. Thirty-five of these HSCT recipients received VD supplementation/therapy until 30 days post-transplantation and were included in our analysis as cohort 1. Thereafter, 25 other subjects underwent HSCT during the “intervention” period, and these composed cohort 2.

Study demographics and patient characteristics for the 2 cohorts are listed in Table 3. The majority of the patients were young males, mostly Caucasian, with a median pre-transplantation weight of 20 kg. More than 60% of the patients received HSCT for a nonmalignant disorder. The majority of transplants (80%) were allogeneic, and 79% of the patients received cells from an unrelated donor. Sixty-eight percent received a myeloablative conditioning regimen, and in 65% the main stem cell source was bone marrow.

In cohort 1, 18 of 35 patients were VD-insufficient and 17 were VD-sufficient at the start of transplantation. At 30 days after transplantation, 15 of these 35 patients (43%) were VD-sufficient, with a median VD level of 40.5 ng/mL (range, 30 to 48 ng/mL). A median of 133 IU/kg/day (range, 44 to 173 IU/kg/day) of cholecalciferol (vitamin D3) was needed to achieve and maintain a sufficient level in patients starting HSCT with a sufficient VD level.

The remaining 20 patients were VD-insufficient at 30 days post-transplantation, with a median VD level of 23 ng/mL (range, 12.6 to 29 ng/mL) while receiving a median cholecalciferol (vitamin D3) dose of 218 IU/kg/day (range, 113.5 to 402 IU/kg/day) (Table 4).

All of the patients in cohort 1 received TPN during the first month after HSCT, and Table 4 summarizes the enteral VD doses provided in addition to the VD dose given in TPN. In cohort 1, the median VD dose received from TPN was a modest 20 IU/kg/day (range, 15 to 35 IU/kg/day). Only one patient in cohort 1 achieved a supratherapeutic but nontoxic VD level of 70.4 ng/mL.

In cohort 2, 12 of 25 patients were VD-insufficient at the start of transplantation. At 30 days after HSCT, 16 patients (64%) were VD-sufficient, with a median VD level of 40 ng/mL (range, 33 to 49 ng/mL). A median cholecalciferol (vitamin D3) dose of 259 IU/kg/day (range, 71 to 375 IU/kg/day) was needed to maintain a sufficient VD level.

The remaining 9 patients were VD-insufficient at 30 days post-transplantation, with a median VD level of 26 ng/mL (range, 22 to 28 ng/ml) while receiving a median cholecalciferol (vitamin D3) dose of 330 IU/kg/day (range, 255 to 418 IU/kg/day) (Table 4). Six patients in cohort 2 received <100 IU/kg/day, 4 by physician choice and 2 large adolescents (>80 kg). All but 1 of these 6 patients were VD-insufficient post-transplantation. Only 1 patient in cohort 2 achieved a supratherapeutic but nontoxic VD level of 105 ng/mL. All patients in cohort 2 received TPN during the first month post-transplantation, at a median dose from TPN of 22 IU/kg/day (range, 14 to 33 IU/kg/day). Table 4 summarizes enteral VD doses provided in addition to the VD dose given in TPN.

DISCUSSION

Despite aggressive monitoring and VD supplementation, we found that therapeutic VD levels are difficult to achieve and maintain in HSCT patients, especially during the early post-transplantation period. As demonstrated by our cohort 1 (preintervention) analysis, National Kidney Foundation guidelines for VD insufficiency treatment are inadequate for HSCT recipients in early post-transplantation period. Only 43% of our HSCT recipients achieved a sufficient VD level of ≥30 ng/mL while receiving as much as 200 IU/kg/day of cholecalciferol (vitamin D3) as enteral therapy.

Cohort 2 (intervention cohort) used data obtained from cohort 1 and were uniformly prescribed high-dose VD therapy at the start of transplantation, with a target dose of at least 200 IU/kg/day for all patients with a pretransplantation VD level <60 ng/mL. It should be noted, however, that dosing varied considerably among patients, because weight categories (eg, 11 to 50 kg) were used, not a dose per kilogram for each case. Cohort 2 patients received a median cholecalciferol (vitamin D3) dose of 260 IU/kg/day enterally in addition to standard VD supplementation in TPN. Despite our proactive treatment strategy and this significant increase in VD doses, only 64% of HSCT recipients achieved or sustained a therapeutic VD level ≥30 ng/mL. Only 1 patient in each cohort achieved a supratherapeutic

VD level significantly below the toxic range. No patient exhibited signs or symptoms of VD toxicity.

It is important to note that VD monitoring is not commonly done in all institutions, and that current clinical practices offer 1 vial of multivitamins containing 400 IU/day of VD in TPN for patients weighing >3 kg. This dose is not adjusted for patient size, so whereas a 4-kg baby will receive 100 IU/kg/day of VD, a 100-kg young adult will receive only 4 IU/kg/day. All of our study patients received TPN during the first month after transplantation, along with 400 IU of VD per day. This translated into approximately 20 IU/kg/day of VD received by this mode of administration and constitutes <10% of the additional enteral dose given.

Currently recommended VD supplementation doses of 400 to 600 IU/day are applicable to individuals who have adequate sun exposure and good nutrition that provide the rest of the needed amount for the total daily VD requirement of 2000 to 3000 IU from all sources. However, the majority of HSCT recipients during the first month post-transplantation are not able to receive these additional sources of VD, owing to transplant-associated illness, sun exposure restrictions, and impaired nutrient absorption [10]. Standard doses of multivitamins delivered in TPN are inadequate to maintain sufficient VD levels in HSCT recipients. In addition, many patients are already VD-deficient at the start of the transplantation process [1,11]. The cushingoid body habitus often observed in a HSCT population also increases VD supplementation needs [12]. In addition, medications commonly used in HSCT recipients, including glucocorticoids, azoles, calcineurin inhibitors, sirolimus, and mycophenolate mofetil, affect VD metabolism [13]. The Endocrine Society's clinical practice guideline, summarized by Holick et al. [9], outlines age, sex, and VD deficiency risk-adjusted recommendations that include daily requirements for VD-deficient subjects and also tolerable upper VD dosage limits for particular risk groups. It also has been suggested that obese children and adults, as well as individuals receiving anticonvulsants, glucocorticoids, or antifungals, should be given at least 2 to 3 times higher VD doses than recommended for their age group to meet VD needs [9]. It is important to note that VD produced in the skin may last twice as long in the blood compared with ingested VD, a fact that is very relevant in a transplantation population that has limited sun exposure.

The Institute of Medicine reports 2000 IU/day as the upper VD supplementation limit, but there is little evidence of toxicity unless doses of 10,000 IU/day of vitamin D3 or 25(OH)D levels of 150 ng/mL are exceeded [14,15]. Veugelers et al. [16] performed a meta-analysis of 108 published reports on VD supplementation and VD status analyzing 13,987 observations of participants, and reported that 2909 IU/day of VD is needed to achieve a serum 25(OH)D concentration of ≥20 ng/mL in 97.5% of healthy individuals. For normal weight, overweight, and obese VD recipients, this dose was 3094, 4450, and 7248 IU/day, respectively [16]. This would translate to approximately 50 IU/kg/day for an adult individual. There are no comparable data reported in children, especially those with chronic illness, including HSCT recipients.

Our data provide some reassurance that it would be quite difficult to reach a toxic level of VD in the early post-transplantation period, especially if the patient is being closely monitored. Fifteen years of data from the National Poison Data System (retrospective

analysis) on 25,397 human exposures of VD overdose reported to US poison centers showed a very low incidence of severe cases of VD ingestion (0.02%), and no significant severe morbidity or mortality [17]. VD intoxication, presenting with hypercalcemia or renal stones, may develop with a serum 25(OH)D level >150 ng/mL; thus, for safety reasons, the VD level should not exceed 100 ng/mL during long-term therapy.

Despite our best efforts to provide systematic monitoring and administration of much higher than recommended VD doses, a large proportion of our patients remained VD-insufficient. It is very likely that absorption and metabolism are significantly affected during the early post-transplantation period, altering blood levels of the vitamin. It is known that along with bone health, VD can contribute to T cell–mediated disease states and may affect the recovery of immune function, incidence of graft-versus-host disease, and overall outcomes after HSCT [1,18–20]. In addition, compliance with therapy will likely suffer in ill HSCT recipients, particularly with the need for frequent administration and dose escalation. Ideally, to provide optimal VD status, body stores should be optimized before proceeding to the transplantation process, challenging us to search for alternative ways to provide this essential vitamin. A single mega-dose VD therapy (also known as Stoss therapy) has been evaluated in other chronic illnesses, including cystic fibrosis, and could provide an alternative option for patients scheduled to undergo HSCT [21]. Prospective studies are currently underway in our institution with the goal of determining the safety and efficacy of Stoss therapy in HSCT recipients.

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Table 1

Recommended Supplementation for VD Insufficiency/Deficiency for Infants, Children, and Adolescents (Used for Cohort 1)

Serum 25-Hydroxy VD Level Pre-HSCT (Baseline), ng/mL*	Cholecalciferol (Vitamin D3) Dose Prescribed at the Start of HSCT
16–30	2000 IU/d orally or enterally (or 50,000 IU every 4 wk)
5–15	4000 IU/d orally or enterally (or 50,000 IU every other wk) for 12 wk
<5	8000 IU/d orally or enterally (or 50,000 IU/wk) for 4 wk, then 4000 IU/d (or 50,000 IU/twice per mo) for 2 mo

*Adopted from National Kidney Foundation guidelines.

Table 2

Cholecalciferol (Vitamin D3) Dosing for HSCT Recipients with Pre-transplantation Serum 25(OH)D Level <60 ng/mL (Used in Cohort 2)*

Weight, kg	Weekly Dose, IU	Daily Dose, IU/kg
5–10	15,000	215–430
11–50	50,000	140–700
51–70	70,000	140–200
71–100	100,000	140–200

*Weekly cholecalciferol dose was proposed based on vitamin D requirements for cohort 1 and is estimated to provide a cholecalciferol dose of IU/kg/d listed in the Daily Dose column.

Table 3

Demographic Data and Patient Characteristics

	Cohort 1 (n = 35)	Cohort 2 (n = 25)
Male sex, n (%)	20 (57)	14 (56)
Age, yr, median (range)	6 (2.1–9.5)	4 (1.7–8.2)
Weight, kg, median (range)	20 (12.3–29)	17.5 kg (11.9–24.9)
Race, n (%)		
Caucasian	30 (86)	23 (92)
African American	4 (11)	1 (4)
Asian	1 (3)	1 (4)
Diagnosis, n (%)		
Malignancy	9 (25.7)	11 (44)
Immunodeficiency	7 (20)	6 (24)
Benign hematology	9 (25.7)	3 (12)
Bone marrow failures	7 (20)	4 (16)
Genetic/metabolic	3 (8.6)	1 (4)
Transplant type, n (%)		
Allogeneic	33 (94.3)	17 (68)
Autologous	2 (5.7)	8 (32)
Conditioning, n (%)		
Myeloablative	21 (60)	19 (76)
Reduced intensity	14 (40)	6 (24)
Stem cell source, n (%)		
Bone marrow	27 (77)	13 (52)
Peripheral blood	4 (11.5)	9 (36)
Cord	4 (11.5)	3 (12)
HLA match, n/N (%)		
Fully matched	20/33 (60.6)	8/17 (47)
Mismatched	13/33 (39.4)	9/17 (53)
Donor, n/N (%)		
Related	8/33 (24.2)	3/17 (17.6)
Unrelated	25/33 (75.8)	14/17 (82.4)

Table 4

Cholecalciferol (Vitamin D3) Doses Required to Achieve or Maintain Sufficient VD Level at 30 d after Transplantation

Cohort	Insufficient VD Pretransplantation, IU/kg/d, median (range)	Sufficient VD Pretransplantation, IU/kg/d, median (range)
Cohort 1 (n = 35)		
Insufficient VD post-transplantation	188 (42–199); n = 10	157 (94–218); n = 10
Sufficient VD post-transplantation	218 (114–402); n = 8	133 (44–173); n = 7
Cohort 2 (n = 25)		
Insufficient VD post-transplantation	266 (63–484); n = 4	260 (160–600); n = 5
Sufficient VD post-transplantation	330 (255–418); n = 8	259 (71–375); n = 8