25-Hydroxyvitamin D Concentrations & Overall Survival in Autologous Bone Marrow Transplant Patients

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MSN CANDIDATE 2014
MASTERS THESIS PRESENTATION
Integrating Research Institutions

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Nutrition & Exercise Science Department

SEATTLE CANCER CARE ALLIANCE
Medical Nutrition Therapy, Transplant

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- Gary Schoch
  - Clinical Research Division, Transplant Services, Fred Hutchinson Cancer Research Center
- Masa Sasagawa, ND
  - Research Institute, Bastyr University
What to expect from this talk:

**BACKGROUND INFORMATION**
- Disease
- Vitamin D
- Autologous Hematopoietic Stem Cell Transplant

**RESEARCH QUESTION & SPECIFIC AIMS**

**STUDY DESIGN & METHODS**

**RESULTS**
- Characterization of the sample
- Vitamin D concentration & Incidence of insufficiency
- Possible contributing factors to vitamin D concentration
- Consequences of vitamin D status

**DISCUSSION & CONCLUSION**
Multiple Myeloma

- Malignant plasma cells in bone marrow and lymphatic system
- Osteolytic lesions:
  - ↑ osteoclast activity (resorption)
  - ↓ osteoblast activity
    - Hypercalcemia
    - Bone loss, bone pain, and fracture
- Vitamin D deficiency is common spread

Is vitamin D supplementation effective as a standard of care for MM patients?

Lymphoma

- Malignant immune-stem cells originating from B- and T-lymphocytes
  - \( \downarrow \) differentiation
    - Immature pre-lymphocytes
    - \( \uparrow \) proliferation signals
- 20+ subtypes
  - Hodgkin Lymphoma
    - Reed-Sternberg cells
  - Non-Hodgkin Lymphoma
    - UVB exposure and reduced NHL risk
    - 25(OH)D insufficiency associated with inferior overall survival

Vitamin D
The Sunshine Vitamin: Synthesis & Retention

- Lipid soluble hormone
  - Endogenous production: UVB exposure
    - Cholecalciferol (D3)
  - Exogenous sources: food and supplements
    - Ergocalciferol (D2) & D3
  - Liver conversion: storage
    - 25-hydroxyvitamin D [25(OH)D]
  - Kidney conversion: biologically active
    - 1,25-dihydroxyvitamin D [1,25(OH)₂D]
      - Vitamin D receptor (VDR) binding
        - Retinoic acid x-receptor complex

Skeletal Functions

Bone mineral metabolism

• ↑ calcium absorption
• ↑ phosphorus absorption
• ↑ calcium resorption
• ↑ calcium reabsorption

Nonskeletal Functions

- Blood sugar control
- Blood pressure regulation
- Parathyroid hormone regulation
- Enhanced immunity
- Reduced risk of certain cancers

A Conditionally Essential Nutrient

- **Sun exposure:** 90% of vitamin D requirement
  - 0.5 minimal erythematous dose (MED)
  - 3000 IU D₃
  - Food sources or dietary supplements

- **Physiologic need**
  - 600IU/day D₃ – *Recommended Dietary Allowance*
  - 1000IU/day D₃ – *Holick M.*
  - 2000IU/day D₃ – *Linus Pauling Institute*

- **D₃ vs. D₂**
  - D₃: 50 – 80% more effective than D₂

- **Insufficiency & deficiency**
  - <30ng/mL *insufficient*
  - <20ng/mL *deficient*
Vitamin D Deficiency: A Global Epidemic

Contributing factors:

- Low dietary intake
- Reduced sun exposure
- Sunscreen use
- Darker skin pigment
- Increased age
- Time of day, year
- Latitude
- Malabsorption
- Obesity
- Reduced liver OR kidney function
- Pharmaceutical use
- Disease, such as lymphoma

Systemic Dysregulation

- **Skeletal homeostasis**
  - Rickets
  - Osteomalacia
  - Multiple myeloma
    - Hypercalcemia, bone destruction, ostealgia, fractures

- **Immunomodulation**
  - ↑ susceptibility to colds, flu, infection
  - Lymphoma
    - Hodgkin and Non-Hodgkin lymphoma
      - Compromised VDR activity
        - ↓ differentiation
        - ↑ proliferation

Hersher, R. Nature Medicine, Spoonful of medicine Mar 01, 2012
Bone Marrow Transplant

- Autologous Hematopoietic Stem Cell Transplant
  - The process of receiving one’s own cells
  - Indicated for MM, Lymphoma (NHL, HD), and other diseases
    - Malignant myelocytes and lymphocytes are the target
    - Not curative for MM or Lymphoma
    - High relapse rate
    - Multiple transplant are common

No correlations between vitamin D status or intake and survival have been made in this population of autologous bone marrow transplant patients

Are there associations between 25-hydroxyvitamin D concentrations and transplant related survival outcomes in individuals undergoing autologous hematopoietic stem cell transplant for the treatment of multiple myeloma or lymphoma?
# 25-Hydroxyvitamin D Concentrations in AHSCT Patients

## Specific Aim: 1
### Characterization
- To characterize vitamin D concentrations in patients prior to autologous hematopoietic stem cell transplant.
- Age
- Demographics (DOB, ethnicity, gender, race, state of residence)
- Anthropometrics (height, weight, BMI, ideal weight, % ideal weight)
- Arrival Date
- Date of diagnosis
- Disease
- Disease subtype
- Vitamin D concentrations pre- and post-transplant
- Vitamin D supplementation

## Specific Aim: 2
### Association
- To determine whether vitamin D concentrations were associated with transplant related parameters and survival outcomes.
- Date of transplant
- Date of death
- Date of last contact
- # Days to survival (transplant date to DLC or DOD)
- Overall Survival (alive/dead)
**Study Design**

- **Total enrolled**
  - n=223

- 31 excluded due to additional non-myeloablative allogeneic transplant
  - n=192

- 52 excluded for not having pre-AHSCT 25(OH)D concentrations drawn or available
  - n=140

- 8 excluded for having diagnoses other than MM or Lymphoma
  - n=132
Study Design

- Race & Ethnicity
- Geographical Location
- BMI & %IBW
- Vitamin D Supplement
- 25(OH)D Concentration & Vitamin D Status
- Time of year diagnosed
- Time of year blood draw

132
MM (n=70) & Lymphoma (n=62)
Chart Abstraction: FHCRC

- FHCRC Transplant Services
  - Demographics
    - Date of birth
    - Gender
    - Height & weight
    - State of primary residence
    - Race
    - Ethnicity
  - Disease & disease subtype
  - Date of transplant
  - Date of death
  - Date of last contact
<table>
<thead>
<tr>
<th>Title</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart Abstraction: Treatment Plan’s &amp; Protocol’s</td>
<td></td>
</tr>
</tbody>
</table>

| SCCA & FHCRC | |

<table>
<thead>
<tr>
<th>Treatment plan 1137</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Multiple myeloma</td>
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<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Disease subtype</th>
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<tr>
<td>1943</td>
<td>Date of diagnosis</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Date of transplant</td>
</tr>
<tr>
<td>Ajay Gopal, MD</td>
<td>Date of death</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>2004</th>
<th>Date of last contact</th>
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<tbody>
<tr>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Bill Bensinger, MD</td>
<td></td>
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</tbody>
</table>
Chart Abstraction: Electronic Medical Records

- **ORCA (Online Record of Clinical Activity), UWMC**
  - Vitamin D concentrations

- **OWL (Online Web Library), SCCA & FHCRC**
  - Arrival Summary, *medical oncologist*
    - Arrival date
    - Diagnosis
    - Date of diagnosis
    - Supplementation
  - Arrival Nutrition Notes, *registered dietitian*
    - Height & weight
    - Ideal weight
    - Percent ideal weight
    - Supplementation
### Table 1. Characterization of Sample by Disease

<table>
<thead>
<tr>
<th></th>
<th>Multiple Myeloma</th>
<th>Lymphoma</th>
<th>P*</th>
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</thead>
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<tr>
<td><strong>Total</strong></td>
<td>70 (53%)</td>
<td>62 (47%)</td>
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<tr>
<td><strong>Timing of diagnosis:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Spring</td>
<td>16 (22.9%)</td>
<td>15 (24.2%)</td>
<td>.912</td>
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<tr>
<td>Summer</td>
<td>18 (25.7%)</td>
<td>17 (27.4%)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>16 (22.9%)</td>
<td>11 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>20 (28.6%)</td>
<td>19 (30.6%)</td>
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</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
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<td>.316</td>
</tr>
<tr>
<td>Male</td>
<td>38 (54%)</td>
<td>39 (63%)</td>
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</tr>
<tr>
<td>Female</td>
<td>32 (46%)</td>
<td>23 (37%)</td>
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<tr>
<td><strong>Age, years:</strong></td>
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<td>.002</td>
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<tr>
<td>&lt;50</td>
<td>6 (9%)</td>
<td>18 (29%)</td>
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<tr>
<td>&gt;50</td>
<td>64 (91%)</td>
<td>44 (71%)</td>
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<tr>
<td><strong>Race:</strong></td>
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<td>.865</td>
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<tr>
<td>White</td>
<td>59 (84%)</td>
<td>54 (87%)</td>
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</tr>
<tr>
<td>Asian</td>
<td>4 (6%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>4 (6%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>American Indian/Native Alaskan</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
<td>.889</td>
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<tr>
<td>Hispanic/Latino</td>
<td>2 (3%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>67 (96%)</td>
<td>60 (97%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*P value from χ² of disease type (MM vs. lymphoma) and covariate
**Vitamin D Status By Disease**

Overall $p = < .001$  
MM $p = < .001$  
Lymphoma $p = < .001$

* $p$ value from t-test of mean pre-transplant 25(OH)D concentrations and vitamin D status (insufficient vs sufficient)
Insufficiency Distributed Evenly Among Age

% Insufficient By Age

Overall

MM

Lymphoma

<50 Years (<30ng/mL)  >50 Years (<30ng/mL)

Overall 48%  52%

MM 54%  46%

Lymphoma 46%  54%

Overall \( p = 0.647 \)  MM \( p = 0.712 \)  Lymphoma \( p = 0.473 \)

*p value from \( \chi^2 \) of age (<50, >50) and vitamin D status (insufficient vs sufficient)
Insufficiency Distributed Evenly Among Gender

Overall $p = 0.456$  MM $p = 0.268$  Lymphoma $p = 0.883$

*p value from $\chi^2$ of gender (male, female) and vitamin D status (insufficient vs sufficient)
Influence on Vitamin D Status by Race & Ethnicity

Distribution of Population By Race and Ethnicity

Race: Overall $p = 0.771$ MM $p = 0.396$ Lymphoma $p = 0.704$
Ethnicity: Overall $p = 0.327$ MM $p = 0.242$ Lymphoma $p = 0.497$

*p value from $\chi^2$ of race, ethnicity, and vitamin D status (insufficient vs sufficient)
Seasonal Influence on Vitamin D Status

% Insufficient by Timing of Blood Draw

Overall $p = 0.659$  MM $p = 0.981$  Lymphoma $p = 0.512$

*p value from $\chi^2$ of timing of blood draw (spring, summer, fall, winter) and vitamin D status (insufficient vs sufficient)
Geographic Location: A Known Factor in Vitamin D Insufficiency

Overall MM Lymphoma

Participant Reported Residence By State

Washington Montana Oregon Alaska Idaho New York

% Insufficient by Geographic Region

Overall p = 0.810 MM p = 0.836

*p value from χ² of geographic location (<37th, >37th) and vitamin D status (insufficient vs sufficient)
Obesity’s Influence on Vitamin D Status

**Body Mass Index**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>MM</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Insufficient (&lt;30ng/mL)</td>
<td>50%</td>
<td>60%</td>
<td>70%</td>
</tr>
</tbody>
</table>

- <25kg/m²: 40%
- >25kg/m²: 70%

**% Ideal Body Weight**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>MM</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Insufficient (&lt;30ng/mL)</td>
<td>40%</td>
<td>50%</td>
<td>60%</td>
</tr>
</tbody>
</table>

- <94%: 50%
- 95-120%: 60%
- >121%: 70%

*BMI: Overall* $p = 0.398$  *MM* $p = 0.687$  *Lymphoma* $p = 0.402$

*%IBW: Overall* $p = 0.400$  *MM* $p = 0.618$  *Lymphoma* $p = 0.192$

*p value from χ² of BMI, %IBW, and vitamin D status (insufficient vs sufficient)*
Supplements Demonstrated to Affect Vitamin D Status

* p value from $\chi^2$ of supplement use and vitamin D status (insufficient vs sufficient)

Overall $p = 0.014$

MM $p = 0.021$

Lymphoma $p = 0.253$
Multivitamins: Highest Contributor to Insufficiency

Overall $p = 0.073$  MM $p = 0.275$  Lymphoma $p = 0.477$

*p value from $\chi^2$ of type of supplement used and vitamin D status (insufficient vs sufficient)*
Survival: A Consequence of 25(OH)D Insufficiency

Overall Survival n=132

HR = 0.99 (95% CI 0.45 to 2.20)
Log-rank P = .997

*p value from Kaplan Meier Survival Curves log-rank of overall survival and vitamin D status (insufficient vs sufficient)
Survival: A Consequence of 25(OH)D Insufficiency

Lymphoma

- Vitamin D insufficient (<30ng/mL)
- Vitamin D sufficient (>30ng/mL)

HR = 0.68 (95% CI, 0.25 to 1.85)
Log-rank $P = .455$

Multiple Myeloma

- Vitamin D insufficient (<30ng/mL)
- Vitamin D sufficient (>30ng/mL)

HR = 1.81 (95% CI, 0.48 to 6.58)
Log-rank $P = .391$

*p value from Kaplan Meier Survival Curves log-rank of overall survival and vitamin D status (insufficient vs sufficient)
Discussion

- The sample is at risk
  - >50% insufficient in vitamin D
    - Mean 25(OH)D concentration of 28.9 ± 10.1 ng/mL
  - 82% over the age of 50
  - 98.5% reside above the 37\textsuperscript{th} parallel
  - 71% overweight or obese by BMI
  - 52% overweight or obese by %IBW

- Factors of the disease:
  - \textdownarrow physical activity
  - \textdownarrow dietary intake
  - \textuparrow need
    - Skeletal homeostasis
    - Immunomodulation
Discussion

- Supplements contribute to ↓ insufficiency
  - Which type? What form? How much?
- 25(OH)D assay and standard reference material standardization
  - No official consensus
- Limitations:
  - Retrospective data
  - Sample size not generalizable to population
  - 3 year follow-up not standard for survival analysis
In Conclusion...

Despite vast differences in 25(OH)D concentrations and vitamin D status vitamin D had no significant impact on survival in autologous bone marrow transplant patients diagnosed with multiple myeloma or lymphoma.

Based on our findings and previous studies it is a reasonable rationale to continue this investigation in a larger sample.
Continuation of Protocol 2629

- Ongoing study at SCCA & FHCRC
  - Patty McDonnell, RD, CSO, RD
  - Available data from 2009 to present
- Additional parameters
  - Fasting Blood Glucose
  - Blood pressure
  - Albumin
  - Urinary protein
  - Lactose dehydrogenase
  - History of bisphosphonate use
  - History of osteoporosis/osteopenia
  - Relapse data
Thank You
Questions?