Bone Health in Hematologic Stem Cell Transplant Patients

Prof David Kendler
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Agenda

• Epidemiology of bone health in hematologic stem cell transplant (HSCT) patients
• Risks for bone loss in HSCT patients
• Bone protection in HSCT patients
• An algorithm for bone health management
Introduction

• Increasing numbers of allogeneic stem cell transplant patients

• Increased survival from improved acute and chronic care

• Bone loss is most rapid in the 1\textsuperscript{st} 3 to 6 months after stem cell transplant with greatest loss at the hip suggesting cortical bone loss

• Fragility fractures remain a long-term serious complication of allogeneic stem cell transplant.
Osteopenia in patients with HSCT

• 29% of HSCT survivors had osteopenia at spine and 52% osteopenia femoral neck (Cohen A et al. JBMR 2004 19:1919 – 1932)

• Early rapid bone loss more so at hip and spine, incompletely recovered at hip

• Cortical bone loss predominates

Grigg AP et al. JCEM 2006, 91:3835 - 3843
Early decreases in BMD in HSCT patients

- 137 HSCT patients between 2011 and 2014 with baseline and day 100 DXA
- Mean lumbar spine day 100 decreases of 3%, total hip of 4.6%, and femoral neck 4.7%. Incidence of osteoporosis increased from 12% to 18% and osteopenia increased from 41% to 50%
- Women have greater loss than men; glucocorticoid was associated with bone loss at total hip
- Day 100 trabecular bone score (TBS) was significantly lower than baseline and lower in patients with glucocorticoid exposure.

Trabecular bone score; an indicator of trabecular bone architecture
BMD and TBS changes after HSCT

• Seoul patients 2009 to 2015
• Decreases in femoral neck (5.48%) and total hip (6.84%) between transplant and twelve-month; TBS stable.
  – 24 patients
• Small increases in lumbar spine and total hip BMD in patients between 12 months and 24 months; TBS stable.
  – 44 patients

Osteoporosis in HSCT patients

- 258 French patients between 2005 and 2016 with baseline, 6 month, and 3 year BMD
- DXA diagnostic of osteoporosis in 17% at baseline, 22.8% at 6 months, and 17.5% at 3 years.
- Incident fractures in 4.1% patients at 6 months and 5.7% of patients at 3 years
- Improvement at spine at 3 years superior to improvements at hip at 3 years.
HSCT and fractures

- 15 year MD Anderson study of 7620 HSCT patients showed 8% incident fractures
- Relation to age, malignancy type, and allogeneic versus autologous transplant
- Fracture risk 8 fold higher than age and sex specific fracture incidence rates from the US population

Pundole X et al. J Clin Oncol 2016; 33 1364 - 1370
HSCT and fractures

- In 4160 Taiwanese cancer patients without HSCT and 1040 patients with HSCT
- Relative risk of fracture 1.4 in the HSCT group
- Vertebral fractures 68% of the fracture events

Lin J et al. 2017 Oncotarget 8, 34811 – 34819
Risks for bone loss in HSCT

Table 1  Risk factors for bone loss pre- and post-stem cell transplantation

<table>
<thead>
<tr>
<th>Pre-HSCT risk factors</th>
<th>Post-HSCT risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex [5]</td>
<td>Calcium and vitamin D insufficiency leading to secondary hyperparathyroidism [7]</td>
</tr>
<tr>
<td></td>
<td>G-CSF treatment [12]</td>
</tr>
<tr>
<td></td>
<td>Renal wasting of calcium or magnesium [13]</td>
</tr>
</tbody>
</table>

- Calcineurin inhibitors
- Interactions between transplant stem cells and bone cells
- Decreased osteocyte viability
- Avascular necrosis in 10% to 20% HSCT survivors

Osteo-immunology

- Crosstalk between the immune system and bone cells
- RANK RANKL OPG responsible for osteoclast formation, function, survival.
  - TNF alpha stimulates RANKL and inhibits osteoblast formation and function
  - IL1, IL7, IL23 also implicated in stimulating osteoclasts
- Trials of mesenchymal stem cells systemic infusion
  - may have benefits to GVHD and directly or indirectly to bone health
- GM-CSF support after chemotherapy and its use to mobilize hematopoietic stem cells
  - may increase the number of osteoclast precursors, enhancing posttransplant bone loss
Hypogonadism

- Ovarian failure occurs in 70% to 90% of young women after HSCT
- Male hypogonadism less common
- Glucocorticoid can lead to central suppression of gonadotropin with secondary hypogonadism
Evaluation of bone health in HSCT patients

• Clinical risk factors
• BMD hip and spine
• Spine radiographs
• Evaluation of secondary cause of bone loss
Risks for bone loss and fracture: pre-existing

- Menopause
- Age
- Prior fracture
- Parental hip fracture
- Smoking
- Alcohol
- Rheumatoid arthritis
- Bone density
- Falls

FRAX has a moderate ability to predict fractures in the HSCT population (Pundole X et al. Arch Osteoporosis 2018. 13:38)
Treatment of HSCT patients: calcium, vitamin D, menopausal hormone therapy

- General nutritional support
- Calcium 1200 mg elemental from combination diet and supplement
- Vitamin D3 2000 IU by supplement, consider loading dose
- Exercise (walking type)
- Menopausal hormone therapy in appropriate patients
Vitamin D deficiency in HSCT patients

- Decreased sun exposure
- GI GVHD may impair vitamin D absorption
- Glucocorticoid, calcineurin inhibitors, renal insufficiency can interfere with vitamin D metabolism
- Median pre-transplant 25 hydroxy vitamin D 40 nmol per litre (16 ng/mL),
  - 70% of patients vitamin D insufficient.
Bisphosphonates post HSCT

- Pamidronate stabilized spine BMD and attenuated femoral neck bone loss (5.1% versus 7.8%) in 99 HSCT patients at 12 months (Kananen K et al. JCEM 2005, 90:3877–3885)
Meta-analysis of bisphosphonate in HSCT

Table 3a. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the lumbar spine at 12 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bisphosphonates</th>
<th></th>
<th>No bisphosphonates</th>
<th></th>
<th>Mean difference</th>
<th>Mean difference</th>
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<td></td>
<td>Mean</td>
<td>s.d.</td>
<td>Total</td>
<td>Mean</td>
<td>s.d.</td>
<td>Total</td>
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<tr>
<td>Grigg et al.</td>
<td>2.3</td>
<td>8</td>
<td>49</td>
<td>-3.3</td>
<td>8</td>
<td>30</td>
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<tr>
<td>Hari et al.</td>
<td>4.1</td>
<td>7</td>
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<td>-5.14</td>
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<td>Jang et al.</td>
<td>0.7</td>
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<td>-6.46</td>
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<td>Kananan et al.</td>
<td>0.25</td>
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<td>Tauchmanova et al.</td>
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<td>Tauchmanova et al.</td>
<td>7.2</td>
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<td>163</td>
<td>100.0%</td>
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</table>

Abbreviation: CI = confidence interval. Test for overall effect: Z = 6.90 (P < 0.00001). Heterogeneity: Tau² = 6.97; χ² = 50.24, d.f. = 6 (P < 0.00001); I² = 88%.

Table 3b. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the femoral neck at 12 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bisphosphonates</th>
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<th>No bisphosphonate</th>
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<th>Mean difference</th>
<th>Mean difference</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
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<td>Total</td>
<td>Mean</td>
<td>s.d.</td>
<td>Total</td>
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<td>Grigg et al.</td>
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<td>Kananen et al.</td>
<td>-4.2</td>
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<td>Tauchmanova et al.</td>
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<td>Total (95% CI)</td>
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<td>143</td>
<td>100.0%</td>
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</table>

Abbreviation: CI = confidence interval. Heterogeneity: Tau² = 0.59; χ² = 7.63, d.f. = 5 (P = 0.18); I² = 34%. Test for overall effect: Z = 11.79 (P < 0.00001).
Pretransplant zoledronic acid randomized trial

- 80 HSCT patients receiving pretransplant ZOL with subsequent day 100, day 180, day 270 infusions according to glucocorticoid or >5% bone loss protocol
- Less bone loss compared to historical controls

Grigg A et al. Bone Marrow Transplantation 2017. 52, 1288 – 1293
Denosumab post HSCT

- 33 female HSCT patients (within 3 years of HSCT) with osteoporosis mean age 52.6 given denosumab 60 mg 6 monthly for 12 months
- Increased spine bone density 4.39%, femoral neck bone density 3.11% and total hip bone density 1.97%

Jeong C et al. Int J Endo 2020 3410921
Other therapies

• **Estrogen**: trials have consistently shown an attenuation of posttransplant bone loss

• **SERM**: milder antiresorptive activity but no studies in HSCT patients

• **PTH and derivatives**: stimulation of bone resorption may release growth factors retained in bone. Teriparatide contraindicated in patients with prior skeletal irradiation or malignant disorders of the skeleton.

• **Romosozumab** has dual action stimulating bone formation and inhibiting resorption. Trials are required.
Management algorithm for HSCT patients

Management algorithm for HSCT patients

Pre HSCT

Patients undergoing allogeneic stem cell transplant*

General measures:
- Regular physical activity
- Vitamin D3 1000-2000 IU/d
- Ca intake 1000-1200 mg/d diet/supplement

Initial Assessment:
- DXA hip and spine, prior osteoporotic fracture, age, menopause status, risk factors
- Ca, PO₄, ALP, TSH, eGFR, 25-OHD

T-score ≥ -1.5 at spine, total hip, femoral neck
T-score < -1.5 at spine, total hip, femoral neck

Management algorithm for HSCT patients

T-score > -1.5 at spine, total hip, femoral neck

T-score < -1.5 at spine, total hip, femoral neck

Pharmacologic intervention
Zoledronic acid
Denosumab possible

Consider pharmacologic intervention if patient taking glucocorticoid for GVHD

Repeat DXA hip and spine

Management algorithm for HSCT patients

- **Day 100**

  - Repeat DXA hip and spine

  - **T-score ≥ -1.5**
    - Repeat DXA and assessment 1 year post transplant

  - **T-score < -1.5**
    - Pharmacologic intervention: Zoledronic acid, Denosumab possible

Summary

• There is increased utilization of HSCT for a variety of hematologic malignancies
• Improvements in acute and chronic care leads to more long-term survivors.
• Bone health is one of the more significant morbidities post HSCT.
• Consistent and more aggressive monitoring and treatment of bone health in HSCT patients is required to improve long-term outcomes.
Q&A

Prof David Kendler
THANK YOU

On behalf of IOF, we thank you for your participation in this webinar
Our vision is a world without fragility fractures, in which healthy mobility is a reality for all.

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