Supportive Care in Multiple Myeloma

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Clinical Myeloma Program
Objectives: review health issues particularly important in living with myeloma

- Neutropenia/Anemia
- Bone health
- Peripheral neuropathy
- Pain management
- Supplements
Normal CBC values

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell count</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>$4.4 - 5.9 \times 10^6$/mcl</td>
</tr>
<tr>
<td>Women</td>
<td>$3.8 - 5.2 \times 10^6$/mcl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>13.3-17.7 g/dl</td>
</tr>
<tr>
<td>Women</td>
<td>11.7-15.7 g/dl</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>40%-52%</td>
</tr>
<tr>
<td>Women</td>
<td>35%-47%</td>
</tr>
<tr>
<td>White blood cell count</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>$3.9 - 11.7 \times 10^3$/mCL</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>White blood cell differential</td>
<td></td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>40%-75%</td>
</tr>
<tr>
<td>Bands</td>
<td>0%-6%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0%-6%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0%-1%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20%-45%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2%-10%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150-400 $\times 10^3$/mCL</td>
</tr>
</tbody>
</table>

What is neutropenia?

*Neutrophils* are infection-fighting white blood cells. They represent the majority of white cells in blood and are short-lived, with a lifespan of only about 6-7 hours.
### Types of White Blood Cells normally found

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Absolute (μL)</th>
<th>Differential (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total WBC</strong></td>
<td>4,500-11,000</td>
<td>100</td>
</tr>
<tr>
<td><strong>Granulocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>3,000-7,000</td>
<td>60-70</td>
</tr>
<tr>
<td>Segmented</td>
<td>2,800-5,600</td>
<td>54-68</td>
</tr>
<tr>
<td>Bands</td>
<td>150-600</td>
<td>3-5</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>50-400</td>
<td>1-5</td>
</tr>
<tr>
<td>Basophils</td>
<td>25-100</td>
<td>0-0.75</td>
</tr>
<tr>
<td><strong>Nongranulocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>100-800</td>
<td>3-7</td>
</tr>
<tr>
<td>Lymphocytes (Immunocytes)</td>
<td>1,000-4,000</td>
<td>25-33</td>
</tr>
<tr>
<td>T cells</td>
<td>800-3,200</td>
<td>80*</td>
</tr>
<tr>
<td>B cells</td>
<td>100-600</td>
<td>10-15*</td>
</tr>
<tr>
<td>Natural killer</td>
<td>50-400</td>
<td>5-10*</td>
</tr>
</tbody>
</table>

*Percent of total lymphocyte count.
Neutropenia

- Defined as either fewer than 1000/μl neutrophils and expected to go down
- Absolute neutrophil count of <500/μl
- Low count increases risk of infections - bacterial, viral, fungal
- Interacts with other risks for infections - steroids, diabetes, general poor health
- Having myeloma by itself increases risk of infection
How often do myeloma treatments cause neutropenia?

- Some forms of Myeloma treatment **always** cause neutropenia (stem cell transplants)
- Some therapies **sometimes** can cause mild neutropenia (oral lenalidomide, pomalidomide, cyclophosphamide)
- Associated with extensive marrow involvement
- Risk of infection is related to how low and how long neutrophils stay down
A person who is neutropenic for a day or two is much less likely to develop an infection than a person who is neutropenic more than a week.
Cellulitis

thrush
Strategies to prevent neutropenia or infections related to neutropenia

- Stem cell reinfusion to minimize length of time white count is low (during transplant)
- Decrease doses of chemotherapy in cycle
- Increase time between cycles of therapy
- Pharmacological doses of G-CSF (filgrastim, pegfilgrastim, TB0-filgrastrim)
- Prophylaxis-antivirals, TMP/sulfa, other antibiotics
- Keep myeloma well controlled
- Keep immunizations up to date (flu, pneumovax, HIB)-Dr Thompson
Anemia

- A common finding in people with myeloma
- Hemoglobin <12, often <10g/dl
- Present in 75% at diagnosis
- Contribution to fatigue uncertain at higher levels (between 10-12 g/dl)

- Use of drugs such as procrit, aranesp are controversial
- Only for pts <10g/dl or on dialysis
- Stop in 6-8 weeks if no improvement
Bone Health
Myeloma and Bone Health

• The explanation for why myeloma cells want to go to bone (and not other places) remains unknown

• Normally fewer than 5% of cells in marrow are plasma cells—just passing through…

• Theories include alteration in myeloma cells causes homing to bone

• Other abnormal cells in marrow attract them or stimulate them
Bone Remodeling Cycle

- Pre-Osteoclasts
- Active Osteoclasts
- Mononuclear Cells
- Pre-Osteoblasts
- Osteoblasts
- Osteocytes

- Resting Bone Surface
- Resorption
- Reversal
- Bone Formation
- Mineralization
Interaction between MM cells and bone marrow environment critical for tumor growth and propagation.
Besides xrays, MRIs, are there other ways to look at bone health?
Blood tests to assess bone health

- About 40% of myeloma patients have an elevation in alkaline phosphatase at diagnosis-this level should be going down with treatment
- Other tests:
  - Bone specific alkaline phosphatase
  - Bone metabolites-propeptides of type I collagen (P1NP, P1CP) and telopeptides of type I collagen (NTX and CTX)-levels go down with improved bone health
  - Not widely measured on a regular basis
**Bone densitometry**

- Results can be presented as g/cm$^2$.
- Z score-density adjusted for sex and age.
- T score-adjusted for sex only, based on “normal young” person.
- $>1$, normal, $\leq -2.5$ SD=osteoporosis.

- Each additional SD away from normal doubles risk of fracture.
- Recommended by the National Osteoporosis Foundation for women $>65$ y.o., pts receiving $> 5$mg prednisone for longer than $3$ mo.
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Country:** US (Caucasian)  
**Name/ID:**

### Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   - **Age:**
   - **Date of Birth:**

2. Sex
   - Male
   - Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture
   - No
   - Yes

6. Parent Fractured Hip
   - No
   - Yes

7. Current Smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units/day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    - Select BMD
    - [Select Value]

[Calculate Button]

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**Weight Conversion**

- **Pounds → kg**
  - Pounds: 125
  - Convert

**Height Conversion**

- **Inches → cm**
  - Inches: 63
  - Convert

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[Footer Link] www.shef.ac.uk/FRAK/tool
• Vitamin D-
  – >50 y.o.-800-1000 IU daily
  – Measure 25 (OH) D level: <20 ng/ml (50nmol/L) defined as deficient; 21-29 insufficient
  – Two forms of oral supplementation-
    • Ergocalciferol D2 or Cholecalciferol (D3); latter better at raising 25 (OH) Vit D
<table>
<thead>
<tr>
<th>25(OH) D Level&lt;sup&gt;bc&lt;/sup&gt; (ng/mL)</th>
<th>Replacement Therapy × 4 Months &amp; Recheck</th>
<th>Maintenance Therapy When Level 30–60 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Ergocalciferol Vitamin D&lt;sub&gt;2&lt;/sub&gt; (requires prescription)</td>
<td>Cholecalciferol Vitamin D&lt;sub&gt;3&lt;/sub&gt; (over-the-counter)</td>
</tr>
<tr>
<td>50,000 IU orally &lt;i&gt;once&lt;/i&gt; weekly</td>
<td>—</td>
<td>2000 IU/d</td>
</tr>
<tr>
<td>10–20</td>
<td>—</td>
<td>2000 IU/d</td>
</tr>
<tr>
<td>20–30</td>
<td>—</td>
<td>1000 IU/d</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Continue patient’s current regimen for all therapies</td>
<td>2000 IU/d</td>
</tr>
</tbody>
</table>

<sup>a</sup>Regimen may NOT be advisable in patients with hypercalcemia, primary hyperparathyroidism, sarcoidosis, or other granulomatous disease.

<sup>b</sup>If levels do not improve after 4 months, consider increasing the dose, and if still not improved, then a gastrointestinal consult should be sought to rule out malabsorption syndrome.

<sup>c</sup>With 25(OH) D <10 ng/mL and bone tenderness, consider diagnosis of osteomalacia and referral to endocrinologist.
• Stop smoking, limit alcohol intake
• Supplements: Institute of Medicine recommends calcium intake, 1200 mg/daily
• Currently available supplements: calcium carbonate require acid for absorption; calcium citrate can be used in pts on antacids
• If you are getting adequate dietary calcium, probably not necessary to take supplements; small risk of developing kidney stones

**EXERCISE IS KEY!** Movement, 30 min daily:
  – Walking, Dancing, Tai Chi, weight training, PT
Proposed mechanisms of action of bisphosphonates
Interaction between MM cells and bone marrow environment critical for tumor growth and propagation

Myeloma cells

Osteoclast

Normal bone
Intravenous bisphosphonates (zoledronic acid, pamidronate) appear to be superior to oral agents (Fosamex); Zometa conferred survival benefit over placebo.
Same pt after rx, transplant, Bisphosphonates, 18 mo later
• Bisphosphonates recommended for all patients with lytic bone disease, monthly for 24 months

• Restart at time of relapse

• After two years of continuous, unclear what should be recommended--? Every 3-6 months
Osteonecrosis of the jaw (ONJ) -

what’s abnormal here is the amount of exposed bone
Figure 1. Duration of exposure prior to clinical presentation

Zometa appears more likely than other bisphosphonates to cause osteonecrosis but all of the agents can; unclear if dental screening is warranted prior to starting bisphosphonates
Other drugs that might help bone?

- Denosumab (Xgeva) vs Zometa trial-ongoing in newly diagnosed myeloma patients

- Results out in two years

- Some data suggests that bortezomib (velcade) and carfilzomib (kyprolis) may also help build bone while treating myeloma
Pain Management
Back pain statistics
(why did they miss my myeloma?)

• 2.4 % of all ER visits (2.4 million annually) for this symptom
• Three months after ER visit, 46% of pts still using pain meds, 42% still had mild to severe pain-so repeat visits don’t necessarily clue in medical staff
• Myeloma back pain-worsens with time, worse with activity, worse as day goes on
• *Myeloma patients-goal is to prevent serious complications-spinal cord compression that could cause paralysis, fractures-severe pain, loss of movement needs immediate intervention*
Immediate Interventions for newly diagnosed pts

- Complete evaluation to understand pain source - x-rays, MRI often very helpful, consultants - orthopedics, neurosurgery
- Sometimes surgery is necessary
- Braces - uncomfortable but can help
- Radiation therapy
- Steroids to reduce inflammation
PAIN MEDICATIONS

- **STEP 1**: acetaminophen, ibuprofen, naproxen, piroxicam, meloxicam, celecoxib, aspirin
- **STEP 2**: “weak” opioid - hydrocodone with acetaminophen (norco, vicodin, lortab); acetaminophen with oxycodone (percocet)
- **STEP 3**: stronger opioids - morphine, oxycodone, fentanyl, oxymorphone, methadone
WHO Model has been criticized: Some useful drugs do not fit into this model well:

- tramadol
- flexeril
- gabapentin, pregabalin

Many myeloma patients benefit from drug class combinations:

E.g. long acting morphine + Tylenol+ nortriptyline+gabapentin
Formal tools to assess pain: Brief Pain Inventory

**Brief Pain Inventory (Short Form)**

Date: ____________________ Time: ____________________

Name: ____________________ Last: ______ First: _______ Middle Initial: ______

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   1. Yes
   2. No

2) On the diagram, shade in the area where you feel pain. Put an X on the area that hurts the most.

3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reduction or increase in two points is considered significant; IF YOU ARE OFFERED THE CHANCE TO USE THESE SCALES, DO SO!
What’s the best treatment for pain?

“It may surprise you to hear that, actually, morphine is the best medicine.”
**Opiate Pain Medications**

- **LONG ACTING**: dosed 1-3x daily
  - MS contin
  - Oxycontin
  - Methadone
  - Fentanyl patch

- **SHORT ACTING**: (last 2-6 hours)
  - Morphine IR
  - Oxycodone
  - Hydrocodone/APAP (Vicodin)
  - Hydromorphone (dilaudid)
  - Fentanyl lozenges
  - Oxycodone/APAP (percocet)
• STARTING POINT: combination of long and short acting medications
• Addition of gabapentin, tricyclic (nortriptyline, etc.)
• If you are taking more than 4 extra doses of short acting, need to consider increasing long acting
• If you are too sleepy, long acting should be reduced
• Very severe pain—pain pumps (PCA), implantable pumps, home IV therapy (home bound), single radiation treatment
• Most patients get acclimated to nausea
• Opiates always cause constipation
• Tapering advised when cutting
• Excessive Tylenol may not be healthy for liver
• Patients with very low platelet counts, kidney problems should use aspirin and ibuprofen cautiously BUT THESE DRUGS SHOULD BE CONSIDERED
Peripheral neuropathy
Peripheral Neuropathy

- PN can be caused by many agents, common ones include alcohol, diabetes, chronic renal failure
- Infections such as varicella (shingles), HIV, occasionally EBV, CMV
- Also toxins such as heavy metals (lead, arsenic, mercury)
- Many chemotherapy drugs
- About 10% of people with myeloma have PN before any treatment
Peripheral Neuropathy

- Typical chemotherapy related neuropathy differs from that of other forms of PN
- Glove and stocking distribution
- Generally sensory, i.e. what a person feels, rather than motor, i.e. what a person can functionally do
- Estimates run that over 1/3 of chemotherapy drugs can cause PN
- Risk of PN often dose related, how much drug a pt. receives over time
• In patients with myeloma, several drugs associated with PN:
  • Thalidomide- PN related to both dose and time on continuous treatment
  • Bortezomib-risks for PN development include
    – Intravenous administration
    – Twice weekly versus weekly
    – Combination with other drugs: egg doxorubicin, platinum, lenalidomide, thalidomide
• vincristine: part of VAD regimen, used much less frequently now for myeloma; often improves with time
• Cisplatin-part of DT-PACE regimen-also associated with tinnitus
• “coasting” can occur, i.e. signs and symptoms continue to develop after therapy stops (particularly true for bortezomib)

• Genetic predisposition may occur—estimated that 1% of myeloma patients are extremely susceptible to bortezomib related PN and may experience this after one dose
• ASCO Guidelines for the Treatment of PN
• Examined 250 trials over twenty years; 42 high quality trials selected to see what drugs helped (or didn’t)

• (JCO 4/14/2014)
Not recommended:

- Acetyl-L-carnitine (ALC)
- Amifostine
- Amitriptyline
- CaMg for patients receiving oxaliplatin-based chemotherapy
- Diethyldithio-carbamate (DDTC)
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Nimodipine
- Org 2766
- All-trans-retinoic acid
- rhuLIF

Recommended:

- Duloxetine (Cymbalta)
- Tricyclic antidepressants-nortryptiline (pamelor), amitriptyline
- Gabapentin
- Topical gel-baclofen, amitriptyline, ketamine
Drug alternatives

- Data suggests acupuncture lowers nausea in pts undergoing chemotherapy
- Ask your provider for a referral
- Some insurance plans cover acupuncture
Steroid induced myopathy

- This is defined as weakness that develops in “large muscle groups” related to steroids
- First studied in 1959
- Appears to be more common when fluorinated steroids used, DEXAMETHASONE!
- Any type of steroid can cause this (even inhalers)
• Typically develops in weeks to months
• Acute form also exists (symptoms occur in matter of 5-7 days)
• Symptoms include increasing weakness of upper arms, thighs
• Difficulty rising from a chair, walking up stairs, lifting more than very light objects repetitively
Treatment

- Recovery is possible but takes weeks to months
- Reduce or discontinue steroids whenever possible
- Every other day dosing of steroid
- Change to less toxic form (e.g. dexamethasone to prednisone)
- Aerobic exercise, resistance training
• No medicines appear to be useful
• Ineffective treatments include:
  – Potassium and phosphorus supplements
  – Dilantin (phenytoin)
  – High dose Vitamin E
  – Anabolic steroids (what body builders, athletes use)
SUPPLEMENTS

• IP-6
Figure 2.—Estimated annual out-of-pocket expenditures for alternative therapies vs conventional medical services, United States, 1997. Data are from the Health Care Financing Administration, United States. RBRVS indicates Resource-Based Relative Value Scale.
Use of alternative medications very common among pts receiving chemotherapy

Richardson et al JCO 18:2505, 2000
**Caveats:**
Some supplements may interfere with chemotherapy agents

Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid–based proteasome inhibitors

Encouze B. Golden,1 Philip Y. Lam,2 Adel Kardosh,3 Kevin J. Gaffney,4 Enrique Cadenas,2 Stan G. Louie,5 Nicos A. Petasis,4 Thomas C. Chen,1,5 and Axel H. Schönhthal3

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Blood 2009, 113: 5927
• Diet: eating from the FDA guidelines
• Exercise: 20-30 minutes 3-5x weekly
• Meditation: appears to improve symptoms such as nausea, fatigue
• Other interventions: music, acupuncture, volunteer activities, sun exposure
• Ask your doctor their opinion regarding your supplements
• Make sure they know you are taking them
Thanks!