MULTIPLE MYELOMA

Overview

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Objectives

• Give an overview of Multiple Myeloma
  • Everything I know in 15 minutes

• Explain how genetic information can be used to personalize treatment

• Open time to answer questions you may have
What is Multiple Myeloma??
Blood: From stem cell to the three cell lines

- Blood stem cell
  - Myeloid stem cell
    - Myeloblast
    - Granulocytes (Eosinophils, Basophils, Neutrophils)
    - Red blood cells
  - Lymphoid stem cell
    - Lymphoblast
    - B lymphocyte
    - T lymphocyte
    - Natural killer cell
  - Plasma cell

- White blood cells
- Platelets
Myeloma is a cancer of plasma cells
Causes and Risk Factors

- We don’t know.

- Chronic inflammation and environmental exposures may play a role

- Risk increases with age
Incidence Rates

Myeloma Age-Specific SEER Incidence Rates 2004-2008

Monoclonal Gammopathy of Undetermined Significance (MGUS) to Myeloma
Symptoms

• Some patients have no symptoms at diagnosis (MGUS or smoldering myeloma)
  
  - Follow basic labs including CBC, BMP, Protein Electropheresis (M-spike), Plasma free light chains (kappa, lambda)
  
  - Development of “CRAB” symptoms may lead to more tests and diagnosis of myeloma

• CRAB symptoms
  
  - C: Hypercalcemia
  
  - R: Renal failure
  
  - A: Anemia
  
  - B: Lytic bone lesions
Myeloma Diagnostic Tests

- History and Physical
- CBC/diff, platelets, BUN/Cr, electrolytes
- LDH, Calcium, albumin
- β2 microglobulin, serum free light chain assay, SPEP with immunofixation
- 24 hour urine for total protein, UPEP with immunofixation
- BNP, Troponin, ECG
- Skeletal survey (Not a bone scan!!)
- Bone marrow biopsy and aspirate (unilateral)
  - Flow cytometry, immunohistochemistry
  - Cytogenetics
  - FISH: del(13), del(17p), t(4:14), t(11:14), t(14:16), 1q21
- If clinically indicated
  - MRI (back pain, neurologic abnormalities)
  - CT Scan (avoid contrast)
  - PET/CT (if suspected multiple plasmacytomas or distinguishing smoldering myeloma vs symptomatic MM)
  - Bone densitometry
  - Plasma cell labeling index
  - Suspected amyloid: biopsy relevant tissue for mass spec for AL amyloid
  - Serum viscosity
  - HLA typing
Related Diagnosis – MGUS
(Monoclonal Gammopathy of Unknown Significance)

- Most MGUS diagnoses are made following a work-up for common symptoms and/or lab test abnormalities

- Can predict risk for progression
  - Non IgG kappa
  - M-spike > 1.5
  - Abnormal Free Light chain ratio
- 0.5% - 1% risk per year for 0 risk factors
- 2-3% per year for 2-3 risk factors

- MGUS patients are followed with blood tests every 3-6 months based on risk of progression
Smoldering Myeloma

- M-protein in serum > 3.0

And/or

- Bone marrow clonal plasma cells >10%
- No end organ damage including no bone lesions (No CRAB symptoms)

- Some data to suggest treatment for these patients
  - Prefer close observation
Symptomatic Myeloma

One or more of:

- **C**: Calcium >11.5 g/dL
- **R**: Cr > 2mg/dL
- **A**: Hb <10 g/dL or <2g/dL below normal
- **B**: Lytic lesions (on x-ray or MRI)
- Free light chain ratio >100
- Plasma cells >60% in the bone marrow
- Repeated infections, Amyloidosis
Natural History of Myeloma

1. Clonal expansion
2. MGUS
3. Early myeloma
4. Late myeloma
5. Plasma cell leukemia

Asymptomatic

Symptomatic

MGUS or smoldering myeloma

Active myeloma

Plateau remission

1. Relapse

2. Relapse

First-line therapy

Second-line

Third-line

Refractory relapse
Survival over time

Here is a graph showing 10-year relative survival rates over time for different age groups. The graph includes data from 1984-1986 to 2002-2004. The survival rates are shown for age groups 15-49, 50-59, 60-69, 70-79, and 80+.

The trend indicates an increase in survival rates over the years for all age groups.
Types of Therapy

• Single or combination drug therapy
  • “Novel agents”
    • Lenalidomide, Pomalidomide
    • Bortezomib, Carfilzomib
  • Steroids (Dexamethasone)
• Traditional chemotherapy
  • Melphalan, Doxil, Cyclophosphamide
Types of Therapy

• High-dose chemotherapy + transplant
  • Autologous (standard)
  • Allogeneic (extreme cases)

• Radiation therapy for local disease

• Supportive Care
  • Zometa for bone lytic lesions
## Types of Stem Cell Transplant

<table>
<thead>
<tr>
<th>Type</th>
<th>Source of Stem Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>Patient’s blood or marrow</td>
</tr>
<tr>
<td>• Standard for MM</td>
<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>Donor blood or marrow or umbilical cord blood</td>
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<tr>
<td>Standard and Reduced-intensity</td>
<td></td>
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</tbody>
</table>
Genetics in Myeloma

- Like many cancers, we know that Multiple Myeloma is more than one disease
- The outcome can vary from low to extremely high risk
- Treatments work more or less in different situations (eg. CRBN)
mSMART 2.0: Classification of Active MM

**High-Risk 20%**
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

**Intermediate-Risk 20%**
- FISH
  - t(4;14)*
- Cytogenetic
  - Deletion 13 or hypodiploidy
- PCLI ≥3%

**Standard-Risk 60%**
- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

3 years
4-5 years
8-10 years

SCHUSTER
Primary amyloidosis is a plasma cell disorder that occasionally occurs in people who have plasma cell dyscrasia.

Amyloid deposits of light chain proteins may affect any body tissues or organs, including the heart, nerves, kidneys, liver etc.

Drugs used to treat myeloma patients are also effective against amyloidosis:
- UCHealth guidelines utilize Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD)
- Can lead to improvement in organ function (e.g., >50% in kidney involvement)

For some patients, stem cell transplantation may be a treatment for amyloidosis.
Clinical Trials in the Treatment of Myeloma

**Phase I**
Tests safety

**Phase II**
Tests how well treatment works

**Phase III**
Compares new treatment to standard treatment

Clinical trials are so important!
Together we can open the doors of knowledge, reduce fear and increase hope about *better treatments* and *improved side effect management*. 
Facts about Clinical Trials

- Clinical trials are appropriate for different types of people, depending on the purpose and phase of the trial.
- A growing number of clinical trials are seeking to include older adults.
- Ethnic minorities are less likely to participate in clinical trials; however, they could benefit from access to emerging treatments.
- The more people who take part in clinical trials, the faster we will find better ways to treat myeloma with less side effects.
Summary

• Multiple Myeloma progresses from a precursor state (MGUS)

• Incurable but very treatable

• Survival rates improving dramatically

• Side effects with newer agents allow for better control with less side effects
Questions?
Thank you!
Side Effects of Traditional Chemo

• Decreased blood cell production – “Myelosuppression”
• Mouth and GI effects – Mouth sores, Nausea, Vomiting, Diarrhea
• Fatigue – can be extreme
• Heart effects
• Renal effects
• Infections - Can require hospitalization
• Hair loss
• Rash
Side effects of Novel agents

- IMiDs (Thal, Len, Pom)
  - Teratogenicity
    - Avoid pregnancy
  - Myelosuppression
  - Fatigue
  - DVT/PE
    - All patients should be on an aspirin OR low dose coumadin
Side effects of Proteosome Inhibitors

- Bortezomib, Carfilzomib
  - Peripheral neuropathy
    - Greatly reduced with weekly Velcade compared to twice weekly with same efficacy
  - Diarrhea/GI
  - Fatigue
Vitamins and Supplements

- Very limited data
- Benefit from **exercise** far exceeds any data on supplements
- Mediterranean diet (aka anti-inflammatory diet)
  - Focus on fish, fiber, whole grains, low glycemic index foods, soy, nuts, fruits, vegetables, green tea, flax, probiotic such as yogurt. To avoid partially hydrogenated oils, high-fructose corn syrup as much as possible.
Vitamins and Supplements

- Multivitamin
  - Vitamin D 800 U, Selenium, standard doses of vitamin C and E, B vitamins

- Green tea
  - EGCG 500mg

- Cruciferous vegetables (Broccoli, water crest, etc)
  - Indol-3 carbinol

- Turmeric 1000mg
Wellness

- Physical
- Emotional
- Mental
- Spiritual
- Community
Wellness

• Physical
  • Measurable
  • Interventions: Diet, Exercise, Medications

• Emotional
  • Effect of stress on health (sympathetic nervous system)
  • Stress reduction: Breathing techniques, Yoga / Tai Chi, Exercise
“That old ‘diet and exercise scam’ again!”
Wellness

• Mental
  • Effect of the brain’s neurotransmitters on health
  • Example: symptoms of depression which affect sleep habits, concentration, general energy, sex drive and hope
  • Interventions: Meditation, psychotherapy/counseling, medications
Wellness

- **Spiritual**
  - What gives your life meaning and purpose? (Hint: It’s not lymphoma)
  - Does not have to be religious
  - Examples: Family, work, pet, hobby, faith
  - **Goal: Focus on these, find a doctor to focus on the lymphoma**
Wellness

• Community
  • People in your life, caregivers, support
Wellness

“Wellness as an individual comes about by working within each of these areas in an integrated manner in conjunction with diet and exercise.”

- Dr. Larry Bergstrom