Multiple Myeloma: Diagnosis, Prognosis, and Treatment

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Professor of Oncology
Karmanos Cancer Institute
General Themes

Smoldering Myeloma: Diverging Philosophies

Newly Diagnosed Myeloma: Reign in Spain
- Adding mAbs
- Depth of response
- Preventing early (non-myeloma) deaths

Relapsed Disease: Beyond (IV) Dara
- BCMA
- Molecular profiling

Amyloidosis: It Really ISN’T Myeloma
Start at the Beginning

Multiple Myeloma arises from MGUS
Incidence of MGUS

- Varies according to SEX: M > W
- Varies according to AGE: Olmsted\(^1\)
  - > 50y: 3.2% (~4% if FLCA testing added)\(^2\)
  - > 70y: 5.3%
  - > 85y: 7.5%
- Varies according to ETHNICITY: \(^3,^4\)

“Uncertain Significance”

MGUS

Stepwise Transformation Process

MGUS

\( t(\text{IgH}) \), del13, KRAS, NRAS, NFκB act, del17p, myc

MM

# MGUS and Myeloma Risk

<table>
<thead>
<tr>
<th>Non-IgM MGUS</th>
<th>SMM</th>
<th>MYELOMA¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% Marrow PCs</td>
<td>&gt; 10% Marrow PCs</td>
<td>“CRAB” Criteria</td>
</tr>
<tr>
<td>&lt; 3 g/dL M-protein</td>
<td>≥ 3 g/dL M-protein</td>
<td>≥ 60% Marrow PCs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i/u FLC ratio &gt; 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1 bone lesion MRI/CT</td>
</tr>
</tbody>
</table>

## M-Spike and FLC Ratio

- **M-Spike**
  - > 1.5 g? (☐)
  - § 1.5 g (✓)

- **FLC Ratio**
  - abn? (☐)
  - abn (✓)

- **20-yr PD Risk**
  - 7% (☐)
  - 20% (☐)
  - 7% (☐)
  - 20% (✓)
  - 30% (✓)

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**Karmanos**

CANCER INSTITUTE

Wayne State University
### SMM and Myeloma Risk

<table>
<thead>
<tr>
<th>Non-IgM MGUS</th>
<th>SMM</th>
<th>MYELOMA&lt;sup&gt;1&lt;/sup&gt;</th>
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<td>&lt; 10% Marrow PCs</td>
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#### Mayo SMM Risk Factors
1. > 10% BMPCs
2. > 3 g/dL M-spike
3. FLC ratio > 8:1

#### Mayo SMM Risk Factors

<table>
<thead>
<tr>
<th># Mayo Criteria</th>
<th>5-yr PD risk&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>&lt;u&gt;76%&lt;/u&gt;</td>
</tr>
</tbody>
</table>

#### PETHEMA SMM Risk Factors
1. > 95% abn PCs (flow)
2. Immunoparesis

<table>
<thead>
<tr>
<th># PETHEMA Criteria</th>
<th>5-yr PD risk&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4%</td>
</tr>
<tr>
<td>1</td>
<td>&lt;u&gt;46%&lt;/u&gt;</td>
</tr>
<tr>
<td>2</td>
<td>72%</td>
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</tbody>
</table>

SMM: New Mayo Risk Groups

NEW Mayo SMM Risk Factors
1. > 20% BMPCs
2. > 2 g/dL M-spike
3. FLC ratio > 20

<table>
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<tr>
<th>Mayo Criteria</th>
<th>5-yr PD risk(^1)</th>
</tr>
</thead>
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<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
</tr>
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<td>3</td>
<td>76%</td>
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Lakshman, et al Abstr #4384

Philosophies Regarding HR SMM

- Close observation (q 3-4 mos) “STANDARD”
- Definitive Rx to eradicate clone(s) “CURE”
- Less intense Rx to delay PD “SUPPRESS”

**Centaurus**
Hofmeister #510

- **Daratumumab 16 mg/kg**
- **8-week cycles**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Q wk</th>
<th>C2-3</th>
<th>C4-7</th>
<th>Up to C20</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Q wk</td>
<td>Q 2wk</td>
<td>Q 4wk</td>
<td>Q 8 wk</td>
</tr>
<tr>
<td>I</td>
<td>C1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Q wk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ORR:** 38-56%
**CR/sCR:** 0-4%

**“SUPPRESS”**

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**GEM-CESAR**
Mateos #402

- **KRd**
- **ACST**
- **KRd**
- **Rd**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>6 cycles</th>
<th>2 cycles</th>
<th>24 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>90*</td>
<td>60</td>
<td>35</td>
</tr>
</tbody>
</table>

- **Cycles**
  - 30 non-CRAB MM

- **ORR:** 100%
- **CR/sCR:** 45%
- **MRD(-):** 31%

**“CURE”**

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**B A R B A R A  A N N**
Cancer Institute
Wayne State University

**Karmananos**
Pre-Symptomatic Plasma Cell Dyscrasias: Conclusions

- MGUS & SMM are by definition asymptomatic
- Risk of progression to MM can be quantified
- Standard of care is observation
  - Treatment on clinical trials only
- MGUS can progress to other conditions
  - Particularly IgM type (NHL)
Newly Diagnosed Myeloma
How Do We Risk Stratify?

- Age, performance status
- International Staging System (ISS)
- Genetic abnormalities
  - Metaphase cytogenetics
  - FISH
- Gene expression profiling

FISH = fluorescence in situ hybridization.
ISS for *Symptomatic* Myeloma

Stage I
- B2MG < 3.5 & Alb > 3.5
- Lab Criteria
- Med. Survival: 62 (58, 65)

Stage II
- Not ISS 1 or 3
- Lab Criteria
- Med. Survival: 44 (42, 45)

Stage III
- B2MG > 5.5
- Lab Criteria
- Med. Survival: 29 (26, 32)

Cytogenetics Delineate Risk...

**High-Risk**
- Del 17p
- t(14;16)
- t(14;20)

**Intermediate-Risk**
- t(4;14)
- 1q gain
- Del 13 (karyotype)
- Hypodiploidy
- Complex karyotype

**Low-Risk**
- All others
- Trisomies
- t(11;14)
- t(6;14)
Influence of t(4;14), del(17p) and β2M on Overall Survival (N=513)

- Low β2M ± del(13) (n=155)
- del 13q no t(4;14), or del 17p, normal β2M (n=110)
- High β2M but no t(4;14), del 17p, or del 13 (n=74)
- High β2M and del 13 no t(4;14), or del 17p (n=69)
- Low β2M and t(4;14) or del 17p (n=63)
- High β2M and t(4;14) or del 17p

## R-ISS (2015)

<table>
<thead>
<tr>
<th>R-ISS STAGE</th>
<th>CRITERIA</th>
<th>5-yr OS%</th>
<th>5-yr PFS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B2MG &lt; 3.5 ALB &gt; 3.5 No HR CA LDH ≤ ULN</td>
<td>82%</td>
<td>55%</td>
</tr>
<tr>
<td>II</td>
<td>Neither I nor III</td>
<td>62%</td>
<td>36%</td>
</tr>
<tr>
<td>III</td>
<td>B2 MG &gt; 5.5 and (HR CA or High LDH)</td>
<td>40%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Combinations in the Up-Front Treatment of Multiple Myeloma

**Why RVD?**

**Clinical Trial S0777**
*Lancet 2017*

**Key eligibility criteria**
- Active myeloma (CRAB)
- Measurable disease
- No prior therapy
- ≤ 2 wks of prior dex
- Good performance status
- No prior malignancy > 5 y

**Randomize**
(n = 261)

**Induction**
(Eight 21-day cycles)
- **BTZ:** 1.3 mg/m² IV d 1, 4, 8 and 11
- **LEN:** 25 mg/d on d 1-14
- **DEX:** 20 mg/d on d 1, 2, 4, 5, 8, 9, 11 and 12

**All pts:** Aspirin
**VRd pts:** Acyclovir

**Rd Maintenance**
(28-day cycles)
- **LEN:** 25 mg d1-21
- **DEX:** 40 mg/wk

**Induction**
(Six 28-day cycles)
- **LEN:** 25 mg/d on d 1-21
- **DEX:** 40 mg/day on days 1, 8, 15 and 22

**Endpoints:**
1°: Progression Free Survival
2°: Overall Survival, Overall Response Rate, Safety
Why Transplant?

Clinical Trial IFM2009
*New Engl J Med 2017*

### Key eligibility criteria
- Active myeloma (CRAB)
- Measurable disease
- No prior therapy
- Age < 65 yo
- Good performance status

#### Randomize

**R** (n = 350)

- **INDUCTION**
  - RVD x 3
  - Collect stem cells

- **CONSOLIDATION**
  - ASCT + RVD x 2

- **MAINTENANCE**
  - Rd Maintenance (28-day cycles)
  - LEN: 15 mg/d x 1 yr

- All pts: Aspirin and Acyclovir

**Endpoints:**
1°: Progression Free Survival
2°: Overall Survival, Overall Response Rate (Others)
Why NOT Allo-Transplant?

- Donor transplant, *potentially* curative
- Higher risk of complications (GVHD)
- Younger, ultra-high risk patients

2015 (HHS/HRSA):
- Allo-Transplant: 190
- Standard Rx (Auto): 7368
Clinical Trial CALGB 100104
*Lancet Haematol 2017*

- Induction Therapy + ASCT

- Randomize
  - Len 10-15 mg
  - Placebo

  (n = 231)

(n = 229)

Clinical Trial RV-MM-EMN-441
*Lancet Oncol 2015*

- RCD vs ASCT

- Randomize
  - Len 10 mg x 21/28 d
  - Prednisone 50 mg qod
  - Len 10 mg x 21/28 d

  (n = 117)

(n = 106)

All pts: Aspirin
Not Resting on Our Laurels

RVD → ASCT → LEN MAINT → S1, S2, S3

- KRD
- LEN 2y v PD
- LEN ‘til PD

E1A11 TRIAL
DFCI-2009 TRIAL
GRAFFIN TRIAL
ALCYONE Trial: VMP +/- Dara

NDMM n=706

ASCT-ineligible

1° endpoint

VMP x 9

6-wk cycles

Dara-VMP x 9

4-wk cycles

Dara q4 wk

PD

PD

Mateos, et al. # LBA-4
ALCYONE Trial: VMP +/- Dara

- Not a regimen with applicability in the USA
- “4 vs 3” or “long vs short”?

Mateos, et al. # LBA-4
MRD in Myeloma: Its Coming

PETHEMA/GEM 2012 Trial

NDMM n=458

ORR: 85% 83%
CR/sCR: 39% 49% 58%
MRD(-): 34% 54% 58%

Rosinol, et al. # 2017
NGF and depth of MRD(-)

~50% of pts

Paiva, et al. # 905
Initial Myeloma Rx: Summary

RVd should be considered “standard”
  • Head-to-head winner vs Rd in S0777

ASCT adds to RVd early on
  • ORR, VGPR, PFS, MRD all better with ASCT
  • Long-term benefit of early ASCT TBD

Maintenance therapy improves PFS (OS?)

What’s coming?
  • (V?)Rd+Elo, Rd+Ixazomib, KRd
Not Resting on Our Laurels

- RVD
- ASCT
- LEN MAINT
- KRD
- LEN 2y v PD
- LEN ‘til PD
- D-RVD
- E1A11 TRIAL
- DFCI-2009 TRIAL
- GRIFFIN TRIAL
Thinking About Therapy Beyond First-Line
What's My Line?
Define “Line”

- A pre-defined course of therapy utilizing agents either simultaneously or sequentially
  - Len/Dex
  - Len/Dex → ASCT
  - Len/Vel/Dex (“RVD”) → ASCT → Len/Dex
  - VDT-PACE → ASCT → TD → ASCT → VDT-PACE → LD

- Pts who have had the same # of “lines” of therapy may have had different types or amounts of therapy
Myeloma Rx All Stirred Up

INDUCTION

RVd  CyBorD  Rd  Vd  (KRd)

Early Referral (Store PBSC?)

ASCT

Lenalidomide Bortezomib (Both)

Maint Rx

S1  S2  S3

Early Referral

Elotuzumab Daratumumab Ixazomib Panobinostat Others

?
Approved Regimens

- Rev-Car-Dex
- Rev-Elo-Dex
- Rev-Ninlaro-Dex
- Rev-Dara
- Vel-Dara
- Vel-Doxil-Dex
- Vel-Pano-Dex
- Pom-Dara

How Do We Choose?
Choosing Salvage Therapy

- Previous therapy
- Comorbid conditions
- Time from previous therapy
- Mode of drug administration
- Genetic risk profile
- Potential role of second ASCT
- Is there an appropriate clinical trial?

MoAbs in Myeloma: Mechanisms of Action

Direct Cytotoxicity

Daratumumab  Elotuzumab

Immunostimulation

ADC P  CD38  EAT-2(+)  SLAMF7  EAT-2(-)

CDC

Elotuzumab/Rd (ELOQUENT-2)

Rd-Elo, lenalidomide, dexamethasone, elotuzumab
CASTOR trial (Vel-Dex +/- DARA)


HR: 0.22 (95% CI, 0.14-0.34; P < .0001)
Median: 7.9 months

HR: 0.51 (95% CI, 0.36-0.73; P = 0.0002)
Median: 6.3 months

HR: 0.22 (95% CI, 0.14-0.34; P < .0001)
Median: 9.8 months

CI, confidence interval; Dara, daratumumab; DVd, daratumumab, bortezomib, dexamethasone; HR, hazard ratio; Vd, bortezomib, dexamethasone
Adding Dara Effective in HR-RRMM

- CASTOR and POLLUX trial showed benefit for DARA arms, even in high-risk cyto/FISH

HRMM, high-risk multiple myeloma; ORR, overall response rate
SubQ Daratumumab!

- Dara FDA-approved as Rx for RRMM
  - Monotherapy, IMiDs, bortezomib
  - Long infusions problematic for clinics and pts

DAVO Trial: injected over 3-5 minutes

<table>
<thead>
<tr>
<th>Part</th>
<th>Dosage</th>
<th>Volume</th>
<th>Patients</th>
<th>IRR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>DARA 1200 + rHuPH20</td>
<td>60 mL</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>DARA 1800 + rHuPH20</td>
<td>90 mL</td>
<td>45</td>
<td>15%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>DARA 1800 + rHuPH20</td>
<td>15 mL</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chari #838
MMRC Molecular Profiling

Auclair, et al. # 395
Typical Obstacles to Trials

- Peripheral Neuropathy
- Kidney Dysfunction
- Low Platelets or White Blood Cells
- # of Prior Therapies
- Competitive enrollment (“You took my spot!”)
- Lacking Molecular Target
- Travel Distance
- Insurance Coverage
Relapsed Myeloma: Conclusions

Embarrassment of riches

Selection/sequencing of therapy complex
  • Clinical Trials and Molecular Profiling

Rise of the antibodies:
  • Elotuzumab
  • Daratumumab
  • Isatuximab
  • Pembrolizumab
Antibiotic Prophylaxis in Newly-Diagnosed Myeloma Patients

Current induction regimens ~90% ORR

A small subset of pts still die in <1yr

• Just as likely to be due to non-myeloma causes
• Half of the 61 pts off PETHEMA/GEM 2012 pre-ASCT
• Remember RD vs Rd?

Drayson, et al. # 903
Amyloidosis
AL Amyloidosis: Background

• Clonal plasma cell disorder characterized by the production of misfolded immunoglobulin light chains (rarely, heavy chains)

• May occur concurrently with myeloma

• Must be distinguished from non-AL types of amyloidosis (e.g., ATTR, AA types)
Amyloidosis Organ Injury

Misfolded Light Chains → Toxic Soluble Oligomers → Tissue Fibrils
Primary Amyloidosis

- Widespread tissue deposition
  - Heart
  - Kidney (glomeruli)
  - Nerves (sensory, autonomic)
  - GI (tongue, gut, liver)
  - Vascular (bleeding)
  - Lung
  - Skin
**Treatment Algorithm**

Is this AL type Amyloidosis?

- **N**
  - Non-chemo treatment appropriate for the specific type of amyloidosis

- **Y**
  - Is the patient a potential candidate for stem cell transplant?
    - **N**
      - Consider additional chemotherapy
    - **Y**
      - High dose melphalan & stem cell transplant

Light chain response? (VGPR+)

- **N**
  - Monitor closely
- **Y**
  - Monitor closely OR NEOD001
Amyloidosis: Summary

- Less common clonal plasma cell disease
- Symptoms from abnormal protein toxicity
- Early diagnosis key
  - Heart involvement drives prognosis
- Therapy “borrowed” from myeloma
  - Goal of therapy: reduction of light chains
Thank You

Questions?