Very Good; Stringent or Complete – Navigating the maze of Myeloma Responses

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MYELOMA
• Increasing understanding of disease biology in the last few years
• Deeper and deeper (better) responses
• Long term survival
• Newer drugs
• CHANGING RESPONSE CRITERIA
• NEW REPORT FORM
• PRACTICAL CLINICAL ASSESSMENT vs. FORMAL RESPONSE ASSESSMENT

Objectives
• Myeloma – the disease & its natural history
• Role of Transplantation – Autologous & Allogeneic
• Response Criteria – Definitions
• The MYE form – limitations
• Common Queries
• Questions

Epidemiology of MM
• 20,000 newly diagnosed patients per year
• >60,000 Americans living with MM
• Similar numbers from the EU
• Median Age at diagnosis
  • 70 yrs (>75% are 70yrs or above)
• Remains Incurable
• Higher (almost double) incidence in Americans of African heritage.
  • Increasing survival
• Almost no one under 20 has MM

Normal Plasma Cells arise from B cells circulate all over produce immune globulins

Myeloma Plasma Cells
• Grow, proliferate and infiltrate
• Secrete – Immunoglobulins or Light chains
• “Create space” – dissolve bone osteolysis
• Immune dysfunction
• Deposition of light chains / amyloid – Organ Impairment
Pathological Diagnosis – identification of plasma cells

Structure and Types of Antibodies (also called Immunoglobulins or Ig)

Whole Antibody and Free Light Chain Production by Plasma Cells

Immunoglobulins

- Concept of Clonality in MM
- Malignant plasma cell – is monoclonal
- One plasma cell clone
  - only one type of heavy chain (one of IgG/A/M/D/E)
  - only one type of light chain (either κ or λ)
- Rare exceptions – Biclonal disease
  - 2 different spikes – IgG K and IgA L
- Also oligoclonal reconstitution:
  - After treatment – recovery of immune function

Whole Antibody and Free Light Chain

Plasmacytoma

- Plasmacytoma
  - >2000 plasma cells/cu mm or >20% PC in WBC diff
  - WBC counts & differential count for total plasma cell number
  - Peripheral Smear Report
  - Circulating Plasma Cells seen – THIS IS NOT PLASMA CELL LEUKEMIA

How is disease followed?

- Secretory Myeloma
  - Plasma cells produce chemicals
  - Intact Immunoglobulin Myeloma
    - Has 2 parts – a heavy & a light chain
    - Ig G or A or M (rarely D or E)
    - Light chain kappa or lambda
      - Ig G κ or IgG λ or IgA K or IgA L ....... etc
  - Light Chain Myeloma
    - ONLY makes the light chain – kappa or lambda
      - Light Chains ----- excreted in Urine preferentially
- Non-secretory Myeloma
  - NO Heavy chain NO Light Chain –
    - Bone Marrow Plasma cells are the only measure of disease
Normal Monoclonal Protein in Myeloma

Serum Protein Electrophoresis

Immunofixation: to determine Type of Monoclonal Protein & detect small amounts

Measuring Disease Burden in MM

- Monoclonal Spike
  - Serum - SPEP
  - URINE - 24 h urine EP
- Immunoglobulin Level
- Serum Free Light Chains
  - Kappa .... Mg/L
  - Lambda .... Mg/L
- Beware the Units ...
   - Mg/dl or Mg/L
- K/L ratio

In addition:
Marrow Plasma Cells
Bone Lesions
Plasmacytomas

Terms:
- M spike – specific time honored marker for myeloma. IgG lambda, IgG kappa, IgA lambda etc
  - TRUE MEASURE OF BURDEN IS M Spike (Serum/Urine)
- IgG or IgA or IgM etc – cruder but since the M spike is part of this measurement we can tell which way things are going.
- E.g. IgA is useful to follow MM if the M spike is an IgA M spike and the M spike is not easily measurable.
  - NOT a criterion for disease assessment normally
- Free Light Chains – Another measure of disease burden
- Total protein – really crude measure (NOT used to follow myeloma). Many people get diagnosed when their primary doctor finds an elevated total protein.

Total Protein / IgG or IgA ... / M spike

- Total Protein
- Albumin + Ig (Immunoglobulin)
- Ig – Normal IgG + IgA + IgM + .... Any M protein...

In most persons with untreated MM:
- Total protein & Igs
- Albumin
Common Problems with MYE forms

Assessing Disease Burden
- Serum: Light chains, M spikes and Igs
- Urine 24 hrs for Urine M spike
- Marrow
- Bone lesions

Assessing Response
- CR or no CR
- Immunofixation or SPEP
- 6 week rule?
- When did CR start? -- But doc says it is CR
- We did not do a marrow!
- Did they relapse? .... And when?

MGUS
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
  - Presence of monoclonal protein at concentration of ≤ 3g/dl in serum or urine without evidence of MM
    - Incidence:
      - up to 2% individuals ≥ 50 yr old
      - <3 g/L monoclonal Ig, little or no proteinuria
      - <10% monoclonal bone marrow plasma cells if done
      - Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions
      - No suppression of uninvolved immunoglobulins
      - Observation with treatment beginning at progression

Smoldering MM
- Serum M protein
- Bone marrow plasma cells
- Absence of CRAB
- Not MGUS / MM or plasmacytoma
- Observation, with treatment beginning at disease progression

Diagnosis of Symptomatic Myeloma
- Active MM
  - ≥ 10% PC
  - M spike
- MGUS
  - <3 g M spike
  - OR ≥ 10% PC
- Smoldering MM
  - ≥ 3 g M spike
  - OR ≥ 10% PC
- No anemia, bone lesions, normal calcium and kidney function

ALL MYELOMA IS PRECEDED BY MGUS or SIMILAR LAB ABNORMALITIES

Common Qn:
- When did MM start?
- What is the baseline M spike?

Stepwise Progression to Myeloma

MGUS
(Monoclonal Gammopathy of Unknown Significance)

SOLITARY PLASMACYTOMA
- SMOLDERING MYELOMA
- ACTIVE SYMPTOMATIC MYELOMA
- EXTRAMEDULLARY MYELOMA
- PLASMA CELL LEUKEMIA

Solitary Plasmacytoma

Table 4 Solitary plasmacytoma of bone

definition of bone plasmacytoma

1. Bony-confirmed monoclonal plasmacytoma of bone in a single site with involvement of 10% of bone marrow plasma cells
2. Bone biopsy shows < 10% of bone marrow plasma cells
3. No other myeloma-related organ dysfunction

Note: M protein is defined as serum ≥ 1.5 g/dl, urine ≥ 30 mg/dl, urine monospecific kappa or lambda < 1.0 g/dl.

Steps:
1. ≤ 3 mg/dl(unknown)
2. ≤ 3 mg/dl(unknown)
3. > 3 mg/dl(unknown)
4. ≤ 3 mg/dl(unknown)
5. > 3 mg/dl(unknown)


Common Qn:
- When did MM start?
- What is the baseline M spike?
**International Staging System for MM**

Beta 2 microglobulin and Albumin - Please search for these values!!

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<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td>I</td>
<td>Serum β2M &lt; 3.5 mg/L Serum albumin ≥ 3.5 g/dl</td>
<td>62 mo</td>
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<tr>
<td>II</td>
<td>Serum β2M &lt; 3.5 mg/l Serum albumin &lt; 3.5 g/dl or Serum β2M 3.5 to &lt; 5.5 mg/L Irrespective of serum albumin</td>
<td>44 mo</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2M ≥ 5.5 mg/L</td>
<td>29 mo</td>
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**Myeloma Insert and Post Transplant Form**

- follows the natural history of this disease

- Initial
  - Myeloma diagnosis – how? When?
  - Disease Burden
  - Organ function -- Symptomatic MM
- Prognostic Factors
  - Therapy pre transplant
  - Response
  - Transplant
  - Post transplant –
    - maintenance / response / relapse

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**Multiple Myeloma**

Course of Disease Treatment and Progression

- Asymptomatic
- Symptomatic
- Active Myeloma
- MGUS or Indolent Myeloma
- Relapsing
- Refractory
- Disease may respond or become refractory at any point
- Marrow Transplant

**IMWG Uniform Response Criteria 2006**

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<td>Near Complete</td>
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<tr>
<td>Complete Response</td>
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</table>
**The New Response Criteria - 2006**

**Protein Electrophoresis and Immunofixation**

- **Immunochromatotype subtype**
  - Heavy chain – G/A/M/D or E
  - Light chain – kappa or lambda
  - Sometimes NONE – Non-secretory

**How much Myeloma?**

- **Crucial** to follow responses over time
  - Protein electrophoresis – measures the monoclonal Ig (M-spike/M-protein)
  - Free-lite test also measures myeloma burden?

**Pretransplant Therapy:**

- Newer drugs:
  - Bortezomib
  - Lenalidomide
  - Thalidomide
- Conventional Chemo:
  - Epoietin Alfa
- Supportive Care:
  - Vertebraplasty
- Radiation Therapy

**What is a line of treatment?**

- One or more cycles of a defined treatment program
- No progression of disease in between
- New line starts when:
  - New agent(s) added/changed for relapse/progression/toxicity
  - After a period of observation when new agent is started for progression/relapse

**Qn:** 62yr old man

- Initial therapy with bortezomib, lenalidomide / dex x 6 cycles,
- followed by stem cell autotransplant and
- lenalidomide after transplant for maintenance

- HOW MANY LINES OF THERAPY HAS HE HAD?
Chromosomal Abnormalities

Were they studied?

Method Used:
- Karyotype (cytogenetics)
- FISH
- Flow cytometry (ploidy)
- PCR

Abnormalities found

Attach report ... please!!

DECIDING ON RESPONSE?

FIRST QUESTION:
WHAT IS THE BASELINE?

PROGRESSION OF DISEASE OR NEW LINE OF TREATMENT – USUALLY MEANS A NEW BASELINE

Now Changed from prior EBMT/IBMTR Response Criteria

Stability of Response - maintained for minimum 6 weeks. BUT STILL NEED CONFIRMATORY TEST.
- E.g. M spike baseline: 2.1 g/dl
  - after Tx: 0.3 (day 100)
  - no labs for next 4 months
  - At 7 months: 0.4 (day 221) Date of best response: ???

What if it was 0.0 (at d221)? – CR at that stage?

Immunofixation and Marrow Aspirate – needed for CR
- OK to accept a prior negative marrow for CR if no progression in between
- Nonsecretory disease– always need marrow aspirate
- At any response level: if some but not all criteria met – downgrade to next lower level of response. e.g. CR criteria met except for immunofixation – response is PR or VGPR

Comparison of Uniform Response Criteria with the EBMT Criteria

- Unchanged categories: CR/PR/PD
- New Category: sCR & VGPR
  - (subcategories of CR & PR)

Clarified: Response Evaluation details

No mandatory wait time but need 2 readings to confirm response

Non-time dependent confirmation of relapse or disease progression
DOR "start time" based on first observation of response
Quantitative immunoglobulin assessment OK when M-protein UNRELIABLE OR UNAVAILABLE – e.g. IgA, IgM. But use the same method through out.
Serum FLC assay in non- or oligo-secretory disease
Comparison of Uniform Response Criteria with the EBMT Criteria

- **Expanded:**
  - Stringent CR – CR with normal free light chains and no marrow disease by flow cytometry
  - VGPR – PR with 90% decline in M spike or detectable only by IFE
  - Clinical Relapse (optional end point) – Two consecutive assessments required
- **SD (TTP Estimates better)**
- **Eliminated:**
  - MR
  - nCR

**Uniform Response Criteria for Disease Progression and Relapse from CR**

- **Progressive Disease:**
  1. Increases ≥25% in serum or urine M-protein
  2. Increase ≥25% in FLC A (Involved – Uninvolved) compared to baseline with absolute increase 10 mg/L
  3. Increase in BM plasma cells ≥10%
  4. New or increasing bone lesions or plasmacytomas
  5. Hypercalcemia (Corrected serum calcium >11.5 mg/dL)
- **Clinical Relapse:**
  - Direct indicators of increasing disease and/or end organ dysfunction (CRAB)
  - Relapse from CR requires at least one of the following:
    1. Reappearance of serum or urine M-protein by immunofixation or electrophoresis.
    2. ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
    3. Any other sign of progression: (new lytic bone lesions, new plasmacytomas, hypercalcemia)

**Using Serum Free Light Chains to measure response:**

1. Use in cases where serum M spike and Urine M spike are unmeasurable (see def) (i.e. M spike unmeasurable at baseline)
2. Identify involved light chain and uninvolved
3. Difference between these (INV – UNINV) at baseline to time of response assessment
4. PR = ≥50% reduction in the difference (INV – UNINV)

**The Free light chain makes things more complicated**

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response, only patients in these two lists and not by the FLC assay FLC response of the free unmeasurable are not applicable to patients with measurable disease in the serum or urine, and to fulfill the requirements of the category stringent CR or partial CR, FLC needs to be assessed. The following list is a guideline for the interpretation of CRAB. Patients with measurable disease in either SPEP or UPEP are not applicable to the response criteria for CRAB.

- If UPEP / SPEP has measurable disease, then FLC is NOT part of response assessment (except sCR)
- FLC needs to be looked at in 3 situations:
  1. NO M spike in SPEP / UPEP
  2. To establish stringent CR
  3. To follow progression when UPEP is not being done

**Guide to Post Transplant Response**

**STEPS:**
1. CR or sCR or Near CR are absolute – don’t worry about what is below.. Otherwise read on ….
2. Identify Baseline (at diagnosis vs. a peak at progression pre transplant)
3. Identify and get values for the following criteria for measurement:
   a. M spike – serum / urine / both
   b. Unmeasurable by a. – FLC? Marrow ?
   c. Any plasmacytomas or bone lesions
   d. Narrow plasma cells

Same steps for assessing response to a line of therapy pre HSCT

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**Maintenance / Extended therapy**

- Not treatment for relapse or progression!
- Planned pre-transplant
- E.g. a protocol that randomizes patients to placebo vs. Lenalidomide after day 100 response assessment – this is maintenance
**Tandem Transplantation**

- Patient has two planned autologous SCT within six months of each other with NO Progression of MM between.
  - Peripheral Blood Stem Cells – Collected once before the initial transplant
  - Half of the stem cells are used for each procedure

This is considered one treatment – pre transplant baseline for calculating response is the baseline prior to Transplant #1.

E.g.
- M spike – 5gm/dl at diagnosis → initial therapy & 4 months later
- M spike – 1 g/dl i.e. 80% decline PR, chemosensitive disease

After Transplant #1 → performed 5 months from diagnosis
M spike – 0.6 g/dl (response is still 5-0.6 NOT 1-0.6)

After Transplant #2 → performed 8 months from diagnosis
M spike – 0.1 g/dl (response is still 5 – 0.1 ie 98%)

**NOTE:**

- All second transplants are NOT tandem
- Tandem transplant is NOT a second transplant performed as a late unplanned transplant for relapse after the first

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**POST TRANSPLANT FORM**

This questionnaire is meant to capture the last disease status on diagnosis to H SCT, that concerned in the reporting interval even if a subsequent disease relapse or progression occurred during the same reporting interval. If a recipient already had been reported as a previous reporting interval, use the best response and check the box to indicate "data previously reported." 

1. Compared to the disease status prior to the preparatory regimen, what was the best response to HSCT since the date of the report? (Specify definition on page 6)
   - CR
   - VGPR
   - PR
   - <5% marrow involvement
   - MR disease (SCz)
   - Progressive disease (PD)
   - Relapse form (CR that ultimately)

2. Laboratory Studies at the Time of Best Response to HSCT
   - First negative IFE date i.e. Retrospective after
   - Second neg IFE > 6wks

3. Plasma cell bone marrow aspirate:
   - Known
   - Not known

4. Quality of response:
   - Good partial response
   - Poor partial response
   - CR
   - VGPR
   - PR
   - <5% marrow involvement
   - MR disease
   - Progressive disease
   - Relapse

5. Transplanted source:
   - Peripheral Blood Stem Cells
   - Bone Marrow
   - Cord Blood

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**Oligoclonal Reconstitution**

- Classic confounder
- His IgA became IgG?
- Can lambda change to kappa after transplant?
- Usually small, more than one M spike occurring in the phase of recovery of immune function

**E.g. Original IgG kappa M spike 3.2 g/dL**
- Day 100 after transplant:
  - SPEP: IgG Kappa 0.14 g/dl, free lambda and nonquantifiable IgA lambda

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**Practical Issues around CR**

- Protein Electrophoresis
  - No suspicion for paraprotein – is this CR?
  - Immunofixation also has to be done to confirm this is CR.
- No IF – no CR (it is only a near CR if an SPEP has shown no paraprotein)
- Needs confirmation or a second SPEP
- Marrow aspirate to confirm CR – PRACTICAL ISSUES

**Immunoassay is essential to call CR**
- Bone Marrow is needed only to confirm a CR
- What if marrow pretransplant had <5% plasma cells and post transplant meets criteria for CR but no marrow done?

- Truly Non secretory MM:
  - Only way to check a response through marrow
- Skeletal Survey – not needed at every time point but if done should not show new lesions.
- MRI / PET – not included in criteria
- Compression fracture – ok – does not preclude CR
- Plasmacytomas need to have regressed

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**Ongoing Response**

**Scenario:**
- PR after transplant Day 100
- Planned Maintenance with drugs
- CR at 1 yr post transplant
  - Qn 1 and its date should update the best response as CR and document the date.
- Patient relapses @ 1.5 yrs post transplant – Best Response since last report - QN1. is CR

**Day 100:**
- PR
**1 year:**
- CR
**2 year:**
- CR
**& go to qn 20**
**Organ Involvement in AL Amyloid**

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<tr>
<th>Organ Involved</th>
<th>Percentage</th>
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<td>Kidney</td>
<td>74%</td>
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<td>Heart</td>
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<td>Liver</td>
<td>28%</td>
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<tr>
<td>Nerve</td>
<td>15%</td>
</tr>
<tr>
<td>GI</td>
<td>8%</td>
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**Tests:**
- Echo
- Liver biopsy
- Alk Phos
- NT Pro BNP
- GI – biopsies / symptoms
- Cardiac MRI
- Chest X ray
- CT scan Lung
- Organ Biopsies

**AL Amyloidosis - Response**

**Classes of Response:**
- Hematological
- Organ

**Criteria:**

**Hematological Response – Very Similar to MM**

- Complete response: Serum and urine amyloidogenic protein < 0.5 g/dl
- Partial response: Serum amyloidogenic protein > 0.5 g/dl or 50% decrease
- Failure: Serum amyloidogenic protein > 2.0 g/dl or no decrease

**Progression:**

- Serum M-component > 2.0 g/dl or > 50% increase
- Urine M-component > 100 mg/dl or > 50% increase

**REMISSION BASED ON:**
- SPEP
- Serum IFE
- UREEP 24 hrs
- Urine IFE
- Marrow
- Free Light Chains: 50% decline

**Marrow not part of PR or Progression**

**Organ RESPONSE and PROGRESSION**

**NOT Commonly seen At 100 days**

- Kidney: common to see decline in proteinuria
- Heart: EF increase, IVS thickness decrease
- Functional Improvement common
- Nerve: Rare improvement in EMG, NCV
- Liver: Reduction in Alk Phos common, Liver Span reduction

**AL Amyloidosis - Organ Involvement**

- 7 major sites of organ involvement:
  - Renal
  - Liver
  - Heart
  - Nerve
  - GI
  - Lung
  - Soft Tissue – (multiple sites)
Specific Form Related Questions on AMY

- Pre TED form:
  - Plasma Cell Disorders (Amyloid not separated out)
    - Disease Status question reflects MM i.e sCR, CR, PR ... etc
    - NOT appropriate / complete since it only measures hematological remission in AMY
    - OK to report hematological status
    - Most patients will be NE/Unk
    - IF no prior treatment -- NE

- When to report organ response?
  - Unlikely to have substantial organ response assessed at D100
  - Most of the response at d100 - functional
  - IF your center looked for organ response, please report
    - e.g U24hr with decline in proteinuria – OK to report

Thank You

- All of you who sent in questions
- Please keep the questions coming