Multiple Myeloma
Newer Response Criteria & New Report Forms

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Why Myeloma?
- Most commonly transplanted hematological malignancy
- Autologous >>> Allogeneic
- Long survival after transplant
- Increasing understanding of disease biology in the last few years
- Newer drugs
- CHANGING RESPONSE CRITERIA & NEW REPORT FORM

Common Problems with MYE forms
- Assessing Disease Burden
  - Light chains, M spikes and Igs
  - Urine 24 hrs
  - Free Lite Chains and Urine light chains
- Assessing Response
  - CR or no CR
  - Immunofixation or SPEP
  - 6 week rule – but when did CR start?
  - But doc says it is CR
  - Did they relapse? .... And when?
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

Immunoglobulins
- Major types of Immune Globulins
  - Heavy Chain - IgG, IgA, IgM, IgD, IgE
  - Light Chains – Kappa or Lambda
- Concept of Clonality in MM
  - Malignant plasma cell – is monoclonal
  - One plasma cell clone ➔
    - only one type of heavy chain (one of Ig –G/A/M/D/E) and
    - only one type of light chain (either κ or λ)
- Rare exceptions – Biclonal disease
  - 2 different spikes – IgG K and IgA L
Epidemiology of MM

- >16000 newly diagnosed patients per year
- 50000 Americans living with MM
- In 2005 – 16570 new cases and 11000 deaths
- Similar numbers from the EU
- Median Age at diagnosis
  - 70 yrs (>75% are 70yrs or above)
- Remains Incurable
- Median Survival from diagnosis 33 months
- Higher (almost double) incidence in Americans of African heritage.
- Almost no one under 20 has MM

Stepwise Progression to Myeloma
MGUS (Monoclonal Gammopathy of Unknown Significance)
- SOLITARY PLASMACYTOMA
- SMOLDERING MYELOMA
- ACTIVE SYMPTOMATIC MYELOMA
- EXTRAMEDULLARY MYELOMA
- PLASMA CELL LEUKEMIA

Prior plasma cell problem?
Plasmacytoma
MGUS
Plasmacytoma

Plasma Cell Leukemia

- Plasma Cell Leukemia
  - >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

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

Symptomatic Multiple Myeloma

- Monoclonal Plasma Cells in Marrow (≥10%) or biopsy proven plasmacytoma
- Monoclonal protein in serum / urine
  - If no monoclonal protein (nonsecretory) – need 30% plasma cells in marrow or plasmacytoma
- Myeloma related organ dysfunction – at least one
  - "CRAB"
    - Calcium (elevated >10.5)
    - Renal (Kidney Disease)
    - Anemia (Hb <10 or 2g/dl below normal)
    - Bone Disease (lytic lesions / advanced osteoporosis)
Smoldering MM
- Serum M protein
- Bone marrow plasma cells
- Absence of CRAB
- Not MGUS / MM or plasmacytoma
- Observation, with treatment beginning at disease progression

Solitary Plasmacytoma

Multiple Myeloma
Course of Disease Treatment and Progression

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
“pathological fracture”  MRI Scan – do I report?

“compression fracture”

Techniques for measuring myeloma burden

- Immune Electrophoresis (SPEP, PEP)
- Immunofixation (IFE)
- Bone Marrow Aspirate or Biopsy

And now a new one....
- Serum Free Light chains
  (FAQ: How do we report it ?)
  No box in current MYE form
  Write in:
  Kappa Light Chains  (mg/L)
  Lambda Light Chains
Electrophoresis - Normal versus Myeloma

Polyclonal

Monoclonal protein

M spike

M protein

M component

Serum Ig levels

Protein Electrophoresis and Immunofixation

- Immunochemical 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
Free Light Chains and Free lite™:
Polyclonal Antibodies to Free Light Chains

Sensitivity Comparison

<table>
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<th>Sensitivity</th>
<th>( \kappa ), mg/L</th>
<th>( \lambda ), mg/L</th>
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<tbody>
<tr>
<td>SPE(^1)</td>
<td>2,000</td>
<td>500</td>
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<tr>
<td>Serum IFE(^1)</td>
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<td>100</td>
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<tr>
<td>UPEP(^2)</td>
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<td>30</td>
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<tr>
<td>Urine IFE(^2)</td>
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<tr>
<td>sFLC assay(^3)</td>
<td>1.2</td>
<td>1.7</td>
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</table>

3 Bradwell et al. Serum Free Light Chain Analysis. 3rd ed.
International Staging System for MM

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
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<td>• I</td>
<td>Serum β2M &lt; 3.5 mg/L</td>
<td>62 mo</td>
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<tr>
<td></td>
<td>Serum albumin ≥ 3.5 g/dl</td>
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<tr>
<td>• II</td>
<td>Serum β2M &lt; 3.5 mg/l</td>
<td>44 mo</td>
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<tr>
<td></td>
<td>Serum albumin &lt; 3.5 g/dl OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum β2M 3.5 to &lt; 5.5 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irrespective of serum albumin</td>
<td></td>
</tr>
<tr>
<td>• III</td>
<td>Serum β2M ≥ 5.5 mg/L</td>
<td>29 mo</td>
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Pretransplant Therapy:
Newer FDA approved drugs included:
- Bortezomib
- Lenalidomide
- Thalidomide

Supportive Care:
- Epoietin Alfa
- Vertebroplasty
- Radiation Therapy

Response to initial therapy
Progression after response?

Chromosomal Abnormalities

Were they studied?

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

Abnormalities found

Attach report please!!
Chromosomal Abnormalities in Myeloma

- Specific chromosome changes in MM
  - Ig translocations
    - 11q13: most common (Cyclin D1, 15-20%)
    - 4p16.3 (FGFR3, MMSET, 12%)
    - 8q24 (c-myc, <10%)
    - 16q23 (c-maf, 5-10%)
    - 6p25 (IRF4, 5%)
  - 13 deletion (Rb, ~50%)

Kuehl WM, Bergsagel PL. Nat Rev Cancer. 2002;2:175

Initial Therapy for MM – prior to transplant

Steps in assessment of transplant response:

What is the baseline to assess response?
- Case #1: Chemotherapy given <6 months prior to transplant. Transplant could be a consolidation of chemotherapy response.
- Baseline – pre-chemotherapy levels
- Case #2: Chemotherapy non-response (e.g. progressed on chemotherapy). Baseline is immediate pre-transplant levels.

Last disease status: cross check with qn 88 & 89

Patients may not have had intermediate pre-Tx staging. Chemotherapy within 6 months and consolidation transplant use the last status post-chemo.
- Chemotherapy <4 months ago and unknown status afterwards did the patient POG 0 or 80?
- If no progression and later transplant = very unusual
Usual Sequence of therapy

Key when transplant is upfront therapy– interval ? - <6m

Another Sequence of therapy

Reference Point: for response assessment
Upfront therapy (incl transplant) – baseline at start of initial Rx
Later transplants (untreated relapse or >6 months from therapy)
– pretransplant M spike is the reference point
Transplant Consolidation of chemotherapy. If within 6 months of chemo – use pre chemo levels as reference.

Current –
Bladé Criteria for Complete and Partial Response

COMPLETE RESPONSE (CR) requires all of the following
- No serum/urine M protein by IFE for ≥ 6 wk
- <5% plasma cells in bone marrow aspirate
- No increase in size of number of lytic bone lesions
- Disappearance of soft tissue plasmacytomas

PARTIAL RESPONSE (PR) requires all of the following
- ≥ 50% reduction in serum M protein ≥ 6 wk
- ≥90% reduction in 24-hr urinary light chain excretion ≥6 wk
- ≥50% reduction in soft tissue plasmacytomas
- No increase in size or number of lytic bone lesions
- Categories of Minimal response, Stable Disease for others
  - EBMT, IMBTR, and ABMTR criteria
Establishing a baseline for assessing response to transplant

EBMT/IBMTR Response Criteria: Problems

- Stability of Response - maintained for minimum 6 weeks – FIXED!
- Immunofixation – needed for CR – Still Needed but a new category of VGPR (very good PR)
- Nonsecretory disease and plasma cell leukemia – need marrow aspirate – Can follow with Free Light
- 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 – Changed to VGPR

The New Response Criteria - 2006
RESPONSE CATEGORIES

Key question:
When & What is the baseline?

Major Changes in the new schema

- No change in CR, PR, PD for patients with secretory MM
- 6 wk wait for confirmation is out!
- Serum free light chains accepted for response
- New categories of response – sCR and VGPR
- New Category of relapse - Clinical Relapse

Comparison of Uniform Response Criteria with the EBMT Criteria

- Unchanged: CR/PR/PD
- Clarified: Response Evaluation
  - Eliminated 6-week mandatory wait time to confirm response
  - Non-time dependant confirmation of relapse or disease progression
  - DOR "start time" based on first observation of PR – TIME more important – Please report dates
  - Quantitative immunoglobulin assessment when M-protein unreliable
  - Serum FLC assay in non- or oligo-secretory disease acceptable
New vs. Old Criteria

- **Expanded:**
  - Stringent CR – CR with normal free light chains and no marrow disease by flow or immunohistochemistry
  - 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 in BM plasma cells ≥10%
  3. New or increasing bone lesions or plasmacytomas
  4. Hypercalcemia (Corrected serum calcium >11.5mg/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. ≥35% 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)

*To be used only if primary end point is DFS
Post Transplant Response

2 new categories!
Stringent CR – improved CR
Very Good PR – improved PR

Oligoclonal Reconstitution

- Classic confounder.
- His IgA became IgG?
- Can lambda change to kappa after transplant?
Maintenance therapy

- Planned pre transplant
- Interferon
- Prednisone
- Thalidomide
- Dexamethasone
- Revlimid (Lenalidomide)
- Velcade

Post Transplant Form

Current Disease Status

- What is the current status of the disease?
- Partial response
- Stable disease
- Progression
- Relapse from complete remission
- Not known
- Not known
- Graft failure
- Relapse

105. Date the response was established:
- Day
- Week

106. Specify the incidence number of this status:
- First
- Second
- Third or higher

107. Plasma cell source:
- Bone marrow
- Peripheral Blood Stem Cells
- Not applicable

Tandem Autologous Stem Cell Transplantation

- Patient has two planned autologous SCT within six months of each other
- Peripheral Blood Stem Cells -- Collected once before the initial transplant
- Half of the cells are used for each procedure

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

E.g.
- M spike – 5 g/dl at diagnosis → initial therapy & 4 months later
- M spike – 1 g/dl i.e. 80% decline Pr, chemosensitive disease
- After Tx #1 → done 5 m from diagnosis
- M spike – 0.6 g/dl (response is still 5 – 0.6 = 1 – 0.6)
- After Tx #2 → done 8 m from diagnosis
- M spike – 0.1 g/dl (response is still 5 – 0.1 = 98%)

So unless the second transplant is a late Tx for relapse – use initial pre Tx #1 baseline for response assessment.
Common Queries

♦ Some Scenarios
  • Discordant Responses or Relapses in different organs
  • Hyposecretory Relapse
  • Renal Escape
  • Timeline of response for upfront transplanted patients
  • Pre transplant Response → post transplant response
    • CR → CCR continuing CR
    • PR → CR or continuing PR
    • MR/SD → PR or CR or MR or SD

Thank You

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