Multiple Myeloma
Linking the clinical course to report forms

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Annual Numbers of Blood and Marrow Transplants Worldwide 1970-2003

Indications for Blood and Marrow Transplantation in North America 2003
Objectives

- Myeloma – Disease biology, Staging and therapy
- Transplantation in Myeloma
- Response Criteria
- The MYE form
- Common Queries
- Questions

Myeloma Disease Biology

- Cancer of Plasma Cells
- Plasma Cells secrete Immune (Monoclonal) Proteins – detected in serum or urine by electrophoresis / IFE
- Rarely nonsecretory type
- Organ dysfunction – ”CRAB”

Plasma Cells come from B cells circulate all over produce immune globulins
Immunoglobulins

- Major types of Immune Globulins
  - IgG, IgA, IgM, IgD, IgE
  - Light Chains – Kappa or Lambda
- Monoclonality
  - One plasma cell clone = only one type of Ig K or L
  - Extremely rare exceptions

Myeloma Plasma Cells

- Grow, proliferate and infiltrate
- Secrete – Immunoglobulins or Light chains
- “Create space” - dissolve bone osteolysis
- Immune dysfunction
- Deposition of light chains / amyloid – Renal Impairment, AL amyloid

Epidemiology of MM

- 15000 newly diagnosed patients per year
- 45000 Americans living with MM
- In 2005 ~ 16000 new cases and 11000 deaths
- Similar numbers from the EU
- Median Age at diagnosis ~ 62 yrs (>75% are 70yrs or above)
- Remains incurable
- Median Survival from diagnosis 33 months
- Higher (almost double) incidence in Americans of African heritage.
Plasmacytoma

Plasma Cell Leukemia versus Circulating Plasma Cells
- Plasma Cell Leukemia
  - >2000 cells/cu mm
  - WBC counts & differential count for total plasma cell number
- Peripheral Smear Report
  - Circulating Plasma Cells seen - THIS IS NOT PLASMA CELL LEUKEMIA

Clinical Spectrum of Plasma Cell Dyscrasia
- Multiple Myeloma
- Solitary plasmacytoma
- MGUS
- Waldenström’s macroglobulinemia
- Lymphoplasmacytic lymphoma
- Primary amyloidosis
- Macroglobulinemia
- AL amyloidosis
- Cryoglobulinemia
- Heavy chain disease
Malignant: Multiple Myeloma

- Bone marrow plasma cells
- Monoclonal plasma cells in marrow (>10%) or biopsy proven plasmacytoma
- Monoclonal protein in serum / urine
- 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)
- Observation, with treatment beginning at disease 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

Solitary Plasmacytoma

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

Diagnostic Criteria – 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)

Serum M protein

Bone marrow plasma cells

Absence of CRAB

Not MGUS / MM or plasmacytoma

Observation, with treatment beginning at disease progression
MGUS and Plasma Cell Leukemia

- Monoclonal Gammopathy of Undetermined Significance (MGUS)
  - Presence of monoclonal protein at concentration of ≤ 3 g/dl in serum or urine without evidence of MM, Waldenström’s macroglobulinemia, amyloidosis, or other lymphoproliferative disorder
  - 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

Myeloma with Amyloid – not AL amyloid on its own

Techniques for measuring myeloma burden

- Immune Electrophoresis
- Immunofixation
- Bone Marrow Aspirate or Biopsy
- Serum Free Light chains (please ignore for MYE form)
Electrophoresis - Normal versus Myeloma

- Polyclonal
- Monoclonal protein
  - M spike
  - M protein
  - M component

Sometimes the subtype may not have been known at diagnosis but identified later in the course of disease – ok to put it in if known at the time of seeing the form.

Distribution of Monoclonal Proteins in MM

- M protein found in serum or urine or both at time of diagnosis in 97% of patients
- Serum M spike: 80%
- Immunofixation positive: >90%
- Urine presence: 75%
- Ig G: 50%-54%
- Ig A: 20%
- Monoclonal light chain: 16%-<20%
- Ig D: 2%

Conventional Staging: Durie Salmon

1. Serum LDH > 2 U/L
2. Urine protein excretion > 2 g/24 hours
3. Bone marrow plasmacytosis > 60%
4. Serum free light chain > 100 mg/L

Primary Source: Initial marrow biopsy
Not Flow Cytometry
Use Aspirate differential count
Or Biopsy estimate

24 hr Urine Light chain result:
Not 24 hr urine protein excretion
Immuno fixation results on the 24hr urine sample
Reported as xxx mg in 24 hr of k or l light chains
Or mg/dl in which case multiply by volume of urine
e.g. 1.45 mg/dl of lambda light chains & Total urine vol – 1500 mL. So 24hr value = 1.45 * 150 mg.

International Staging System for MM

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<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
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<tr>
<td>I</td>
<td>Serum β2M &lt; 3.5 mg/L, Serum albumin &gt; 3.5 g/dl</td>
<td>62 mo</td>
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<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>
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<td>III</td>
<td>Serum β2M ≥ 5.5 mg/L</td>
<td>29 mo</td>
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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

Usual Sequence of therapy

Key when transplant is upfront therapy: interval < 6m
Usual Sequence of therapy

Transplant maybe later therapy - is at relapse from initial

Myeloma Management – Recent History

- 1962 Melphalan
- 1964 Cyclophosphamide
- 1967 Corticosteroids
- 1969 MP
- 1975 Durie-Salmon staging
- 1976 First trials of complex chemotherapy combinations
- 1983 High-dose melphalan; serum β2-microglobulin for prognosis
- 1986 High-dose Dex; HDT with ACST
- 19882 Twin transplants for MM
- 1984 First autologous transplants; VAD
- 1985 IFN alfa
- 1996 Bisphosphonates
- 1999 Thalidomide; Nonmyeloablative transplants
- 2000 Bortezomib; lenalidomide
- 2005 IMiDs - Lenalidomide; antiangiogenic; arsenic

Usual Agents for Initial Therapy

<table>
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<tr>
<th>Treatment</th>
<th>6a</th>
<th>6b</th>
<th>6c</th>
<th>6d</th>
<th>6e</th>
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Other

Please use this to report: Thalidomide; Lenalidomide; Bortezomib; combinations
Sometimes given for priming alone e.g. Cytoxan—Would now be considered a line of therapy for reporting but important to differentiate during analysis

Please check to tally with Qn 189

Initial date of lowest paraprotein

Autologous Stem Cell Transplantation

- Mobilization and Leukapheresis of Patient Stem Cells
- High Dose Chemotherapy
- Cryopreservation of Patient Stem Cells
- Thawing and infusion of patient stem cells

Tandem Autologous Stem Cell Transplantation

- Patient has two planned autologous SCT within six months of each other
  - HSC -- 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 prior to T#1.

E.g.
- M spike – 5 gm/dl at diagnosis → initial therapy & 4 months later
- M spike – 1.0 gm/dl i.e. 80% decline PR, chemosensitive disease
- After Tx #1 → done 5 m from diagnosis
- M spike – 0.6 gm/dl (response is still 5-0.6 NOT 1-0.6)
- After Tx #2 → done 8 m from diagnosis
- M spike – 0.1 gm/dl (response is still 5 – 0.1 i.e 98%)

So unless the second transplant is a late Tx for relapse – use initial pre Tx#1 levels for response assessment
Continuing CR from before

Last disease status: cross check with qn 88 & 89

Patients may not have had immediate pre Tx staging: Chemo within 6 months and consolidative transplant

Chemo >6 months ago and unknown status thereafter did the patient PROG or REL?

If no progression and later transplant – Very Unusual

Unknown / NE / Other, specify

Probability of Survival after Autologous Transplants for Multiple Myeloma

<table>
<thead>
<tr>
<th>Response Type</th>
<th>N eval</th>
<th>Survival</th>
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<td>Complete Response</td>
<td>1,304</td>
<td>1-yr 91 ± 9%</td>
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<td>3-yr 70 ± 2%</td>
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<td>5-yr 56 ± 3%</td>
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<td>Partial Response</td>
<td>5,016</td>
<td>1-yr 90 ± 1%</td>
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<td>3-yr 66 ± 1%</td>
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<td>5-yr 51 ± 2%</td>
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<td>Minimal Response</td>
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<td>1-yr 86 ± 2%</td>
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<td>3-yr 66 ± 3%</td>
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<td>5-yr 47 ± 5%</td>
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<td>No Response/Stable Disease</td>
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<td>1-yr 86 ± 2%</td>
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<td>3-yr 65 ± 3%</td>
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<td>5-yr 47 ± 6%</td>
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<td>Progressive Disease</td>
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<td>1-yr 77 ± 2%</td>
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<td>3-yr 44 ± 3%</td>
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<td>5-yr 21 ± 4%</td>
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</table>
Bladé Criteria for Complete and Partial Response

Complete response 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 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

- EBMT, IMBTR, and ABMTR criteria

RESPONSE CRITERIA: Ground Rules

- Stability of Response - maintained for minimum 6 weeks
- Immunofixation – needed for CR
- Bone disease – check to ensure stability
- Nonsecretory disease and plasma cell leukemia – 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
Oligoclonal Reconstitution

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

**Complete Remission**

- Absence by Immunofixation Maintained for 6 weeks
- Marrow essential if non-secretory
- Stability of bone lesions

**QUERIES:**

- Immunofixation not done → PR
- Oligoclonal reconstitution is still CR
- Look at original paraprotein !!!

"Too low to quantitate" → PR

Some Key Features of Response

- Immunofixation essential to call CR
- Bone Marrow needed only to confirm a CR
- Upfront Transplant – Baseline comparison for paraprotein level is from before initial therapy (as long as transplant followed such treatment within 6 months)

**Steps in assessment of Transplant response:**

- What is the baseline to assess response?
  - Case #1: Chemo given ≤ 6m prior to transplant? Transplant could then be a consolidation of chemo response.
  - Baseline – pre chemotherapy levels
  - Case #2: Chemo non-response (e.g., progressed on chemo) OR no chemo within 6 months of transplant.
  - Baseline here is immediate pretransplant levels.
Clinical Scenario – CR issue

- Protein Electrophoresis - No suspicion for paraprotein – Immunofixation also has to be done to confirm this is CR.
- No IF – no CR (it is only a PR if an SPEP has shown no paraprotein)
- Remember 6 week stability issue
- Marrow aspirate to confirm? – needed before CR confirmed – Can be omitted if 6 weeks stability criterion met.
- Non secretory MM:
  - Only way to check a response is through serial marrow performed 6 weeks apart!
  - Free light chains not accepted currently
- Skeletal Survey – not needed but if done should not show new lesions.
- MRI – not included
- Compression fracture – ok – does not preclude CR
- Plasmacytomas need to have regressed

**PARTIAL RESPONSE:**

- Serum: 50% or more reduction.
- Urine LC: 90% reduction or to <200mg/24hrs.
- IFE not essential.
- 50% decrease in plasma cells in marrow.

Response scenarios

- PR >50% decline if serum
- >90% decline in urine 24h light chains or if <200mg/24h
  - E.g. 1500mg/day of Urine light chains at baseline and 180 mg24h post treatment. – Still PR
- Needs to be sustained for 6 weeks
- Our forms D100 – will capture the best response in most patients but if a better response happened later – will need to be captured in the 1 year follow-up report

**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 level as reference.
Post Transplant Maintenance Therapy

- Interferon
- Prednisone
- Thalidomide
- Dexamethasone
- Revlimid (Lenalidomide)
- Velcade

Issues:
- Any survival benefit?
- Quality of Life affected?
- Delaying of Relapse versus QOL

Newer Drugs for MM

- Thalidomide (Thalomid, Celgene)
  - PO drug. Used in all stages of treatment
- Bortezomib (Velcade, Millennium)
  - IV drug. Used in all stages of therapy
- Lenalidomide (Revlimid, Celgene)
  - PO drug. In clinical trials for relapsed disease
Common Queries

- When was myeloma diagnosed?
  - Preceding MGUS?
  - Preceding plasmacytoma

- Non-secretory MM?
  - Do not report a light chain or Ig subtype if nonsecretory

Common Queries

- How do I calculate response?
  - Reference points
  - M spike baseline
  - "M spike = M protein = Paraprotein = Myeloma spike"

- Can MM change subtypes?

- Free Lite chains
  - Not being captured now

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
      - HR/SD → PR or CR or HR or SD
Thank You

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