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

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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?

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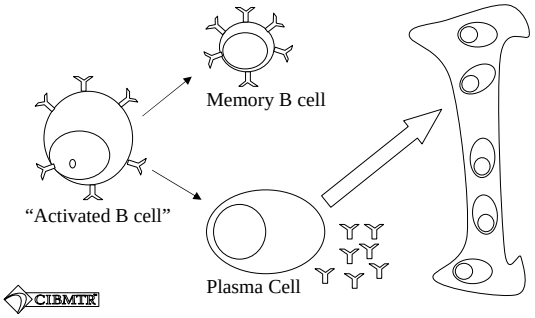
Normal Plasma Cells arise from B cells circulate all over produce immune globulins



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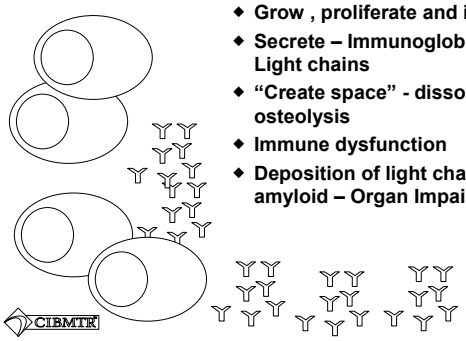
Myeloma Plasma Cells



- **Grow , proliferate and infiltrate**
- **Secrete – Immunoglobulins or Light chains**
- **"Create space" - dissolve bone osteolysis**
- **Immune dysfunction**
- **Deposition of light chains / amyloid – Organ Impairment**

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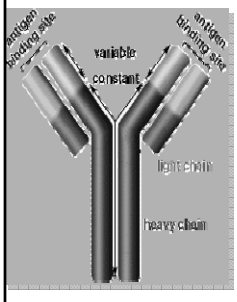
Immunoglobulins



- Major types of Immune Globulins
- **Heavy Chain** - IgG, IgA, IgM, IgD, IgE
- **Light Chains** – Kappa or Lambda

- **<u>Concept of Clonality in MM</u>**
- 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**

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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***

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Stepwise Progression to Myeloma

MGUS (Monoclonal Gammopathy of Unknown Significance)

SOLITARY PLASMACYTOMA

- **SMOLDERING MYELOMA**
  - **ACTIVE SYMPTOMATIC MYELOMA**
    - **EXTRAMEDULLARY MYELOMA**
    - **PLASMA CELL LEUKEMIA**

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Specify disorder(s):

	yes	no	unknown		Month
3.	1 ☐	2 ☐	3 ☐	Prior solitary extramedullary plasmacytoma (in absence of bone marrow findings diagnostic for multiple myeloma or plasma cell leukemia)?	
4.	1 ☐	2 ☐	3 ☐	Prior monoclonal gammopathy of unknown significance (MGUS)?	
5.	1 ☐	2 ☐	3 ☐	Plasma cell leukemia at diagnosis (blood plasma cells > 20% of WBC differential or absolute blood plasma cells > 2.0×10^9/L [$\times 10^3$/mm^3])?	

Prior plasma cell problem?

Plasmacytoma

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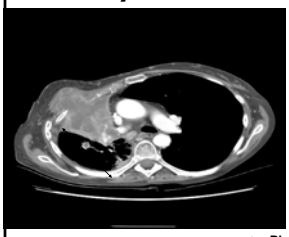
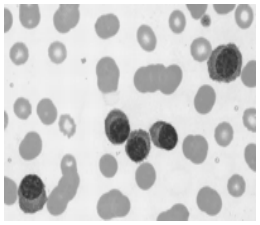
Plasmacytoma



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

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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

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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)

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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

Table 4 Solitary plasmacytoma of bone Diagnostic criteria: all three required

1. Biopsy-proven monoclonal plasmacytoma of bone in a single site only. X-rays and MRI and/or FDG PET imaging (if performed) must be negative outside the primary site. The primary lesion may be associated with a low[a] serum and/or urine M-component
2. The bone marrow contains < 10% monoclonal plasma cells
3. No other myeloma-related organ dysfunction

[a]Low is defined as: serum IgG < 3.5 g/dl; serum IgA < 2.0 g/dl; urine monoclonal kappa or lambda < 1.0 g/24 h.

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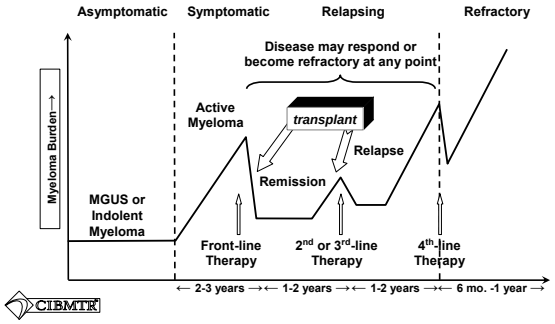
Multiple Myeloma
Course of Disease Treatment and Progression



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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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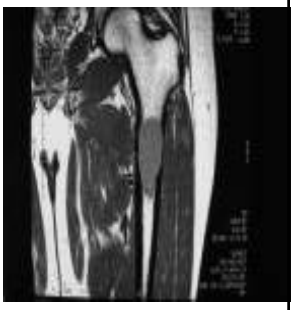
"pathological fracture"

MRI Scan – do I report?



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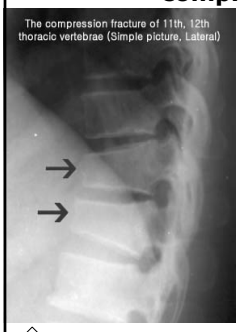
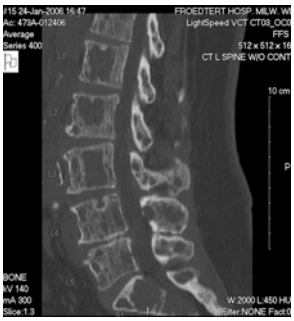
"compression fracture"





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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

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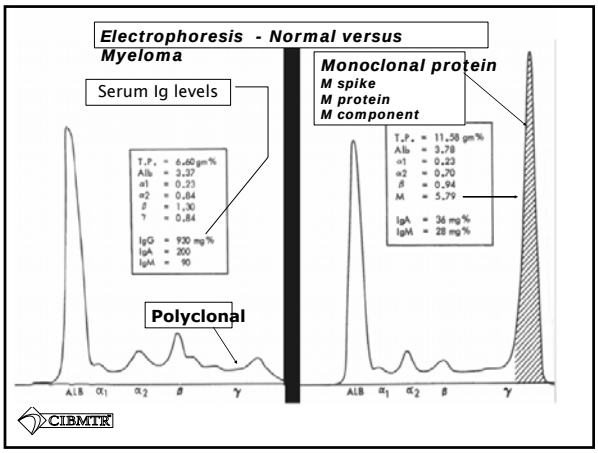

Protein Electrophoresis and Immunofixation

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

Specify the immunochemical type:
1 ☐ non-secretory
2 ☐ secretory → Specify paraproteins present:

Paraprotein	Chain type IgG	IgA	IgM	IgD	IgE	Source Serum	Urine
9. Heavy chain (first paraprotein)	1☐	2☐	3☐	4☐	5☐	1☐	2☐
10. Heavy chain (second paraprotein)	1☐	2☐	3☐	4☐	5☐	1☐	2☐
11. Light chain (first paraprotein)	1☐	2☐	3☐	4☐	5☐	1☐	2☐
12. Light chain (second paraprotein)	1☐	2☐	3☐	4☐	5☐	1☐	2☐

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How much Myeloma?

23. Serum monoclonal Ig (only from electrophoresis)
1 ☐ known → ☐☐☐.☐ 1 ☐ mg/dL 2 ☐ g/dL 3 ☐ g/L
2 ☐ not known
24. Urinary monoclonal light chains:
1 ☐ known → ☐☐☐.☐ g / 24 hours
2 ☐ not known
25. Serum free light chains — kappa (κ):
1 ☐ known → ☐☐☐.☐ mg/dL
2 ☐ not known
26. Serum free light chains — lambda (λ):
1 ☐ known → ☐☐☐.☐ mg/dL
2 ☐ not known

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

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32. Plasma cells in bone marrow (Aspirate): ___ %
33. 1❑ Source (aspirate vs biopsy) unknown 8❑
34. Plasma cells in bone marrow (Biopsy): ___ %
8❑

***Primary Source*:**
Initial Marrow Biopsy
Not Flow Cytometry
Use Aspirate differential count
Or Biopsy estimate

40. Urinary monoclonal light chains: ___ : ___ g/24h
41. Serum β_2-microglobulin:
42. C-reactive protein:
43. Labeling index:

***24 hr Urine Light chain result* :**
Not 24 hr urine protein excretion
***Electrophoresis* results on the 24hr urine sample**
Reported as xxx mg in 24hr of k or l light chains
Or mg/dl in which case multiply by volume of urine
e.g. 145mg/dl of lambda light chains & Total urine vol – 1500 ml.
So 24hr value =145 *150 mg.

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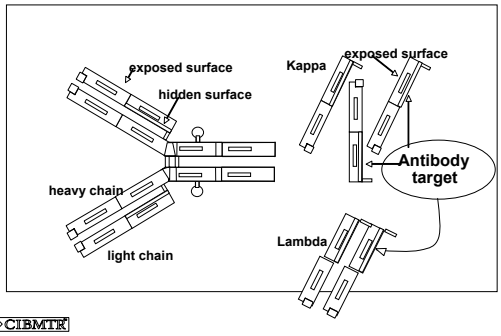
Free Light Chains and Free lite™ :
Polyclonal Antibodies to Free Light Chains



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Sensitivity Comparison

Sensitivity	κ, mg/L	λ, mg/L
SPE[1]	**2,000**	**500**
Serum IFE[1]	**150**	**100**
UPEP[2]	**30**	**30**
Urine IFE[2]	**20**	**20**
sFLC assay[3]	1.2	1.7

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[1] Katzmann et al. *Clin Chem.* 2002;1437–1444.
[2] Beetham et al. *Ann Clin Biochem* 2000;37:581–587.
[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!!!

Stage	Criteria	Median Survival
◆ I	**Serum β2M<3.5 mg/L** **Serum albumin ≥3.5 g/dl**	**62 mo**
◆ II	**Serum β2M <3.5 mg/l** **Serum albumin <3.5 g/dl OR** **Serum β2M 3.5 to <5.5 mg/L** **Irrespective of serum albumin**	**44 mo**
◆ III	**Serum β2M≥5.5 mg/L**	**29 mo**

Greipp PR et al. *J Clin Oncol.* 2005;23:3412

19. Serum albumin:
1 ☐ known → ☐☐.☐ 1 ☐ g/dl 2 ☐ g/L
2 ☐ not known

20. Serum β2 microglobulin:
1 ☐ known → ☐☐☐.☐☐☐☐
2 ☐ not known

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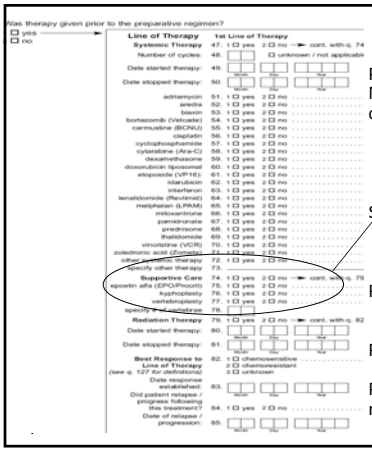


Pretransplant Therapy:
Newer FDA approved drugs included:
- Bortezomib
- Lenalidomide
- Thalidomide

Supportive Care:
- Epoietin Alfa
- Vertebroplasty

Radiation Therapy

Response to initial therapy

Progression after response?

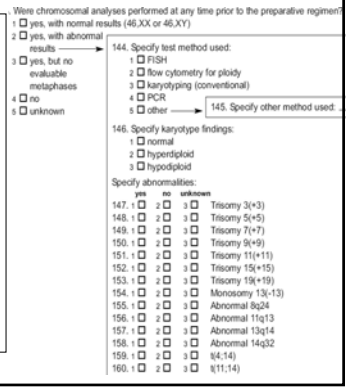
Chromosomal Abnormalities

Were they studied?

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

Abnormalities found

Attach report please!!



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Chromosomal Abnormalites in Myeloma

237.[2] Were cytogenetics done on bone marrow anytime prior to high-dose therapy (conditioning)?

1 ❑ Yes, normal (46,XX or 46,XY)

2 ❑ Yes, but no evaluable metaphases _____

- **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

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Initial Therapy for MM – prior to transplant

55. Was patient treated for multiple myeloma or plasma cell leukemia prior to high-dose therapy (conditioning)?

1 ❑ Yes 0 ❑ No — Go to *Q.189.*[2]

Regimen		1st	2nd
Radiation Therapy:	**57.**	1 ❑ Yes 0 ❑ No	**90.** 1 ❑ Yes 0 ❑ No
Specify sites:	**58.**[2]	_____	**91.**[2] _____
Date started:	**62.**	Month Day Year	**95.** Month Day Year
Chemotherapy:	**64.**	1 ❑ Yes 0 ❑ No	**97.** 1 ❑ Yes 0 ❑ No

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.

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206. Indicate patient's sensitivity of myeloma to chemotherapy prior to conditioning
*(**Q.206 only**: treatment must have been completed ≤6 months prior to transplant)*:

1 ❑ Sensitive (≥50% reduction in Ig level, or ≥90% reduction in urinary light chains in light chain only disease, or ≥50% reduction of plasma cells in bone marrow for nonsecretory myeloma)

2 ❑ Resistant (<50% reduction of Ig level, or <90% reduction in urinary light chains in light chain only disease, or <50% reduction of plasma cells in bone marrow for nonsecretory myeloma)

3 ❑ Not applicable (no chemotherapy, or ended more than 6 months prior to conditioning)

88 ❑ Unknown

Last disease status: ***cross check with*** *qn* ***88 & 89***

207. Indicate patient's disease status of multiple myeloma or plasma cell leukemia immediately prior to conditioning for transplant *(refer to page 7 for definitions)*:

1 ❑ CR

2 ❑ CCR → **Continuing CR from before**

3 ❑ PR

4 ❑ MR (multiple myeloma only)

5 ❑ NR

6 ❑ SD (multiple myeloma only)

7 ❑ REL from CR (untreated)

8 ❑ PROG

80 ❑ NE, specify reason: _____

88 ❑ Unknown

90 ❑ Other, specify: _____

Patients may not have had immediate pre Tx staging:
Chemo within 6 months and consolidative transplant
use the last status post chemo
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

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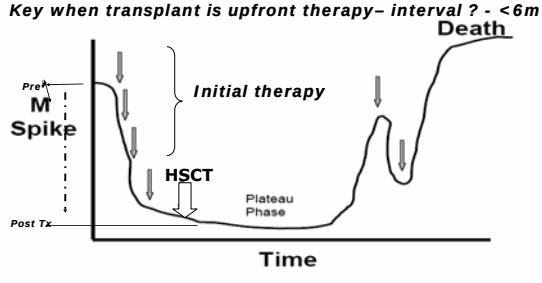
Usual Sequence of therapy

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



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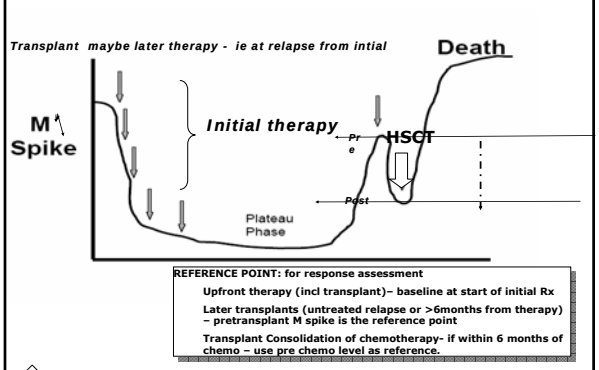
Another Sequence of therapy

Transplant maybe later therapy - ie at relapse from intial



REFERENCE POINT: for response assessment

- **Upfront therapy (incl transplant)– baseline at start of initial Rx**
- **Later transplants (untreated relapse or >6months 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.**

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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 ≥6wk**
- **≥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**
- **Bladé J et al. *Br J Haematol*. 1998;102:1115**

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Establishing a baseline for assessing response to transplant

125. Specify the total number of chemotherapy regimens given prior to the preparative regimen: ☐☐

126. At what point in the disease course was the HSCT performed?

1 ☐ as part of initial therapy for a recipient with no disease progression at any time prior to HSCT

2 ☐ later in the disease course for a recipient with disease progression at any time prior to HSCT

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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**

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The New Response Criteria - 2006

Leukemia (2006) 20, 1467–1473
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www.nature.com/leu

LEADING ARTICLE

International uniform response criteria for multiple myeloma

BGM Durie[1], J-L Harousseau[2], JS Miguel[3], J Bladé[4], B Barlogie[5], K Anderson[6], M Gertz[7], M Dimopoulos[8], J Westin[9], P Sonneveld[10], H Ludwig[11], G Gahrton[12], M Beksac[13], J Crowley[14], A Belch[15], M Boccadaro[16], J Turesson[17], D Joshua[18], D Vesole[19], R Kyle[7], R Alexanian[20], G Tricot[6], M Attal[21], G Merlini[22], R Powles[23], P Richardson[24], K Shimizu[25], P Tosi[26], G Morgan[27] and SV Rajkumar[7] on behalf of the International Myeloma Working Group[28]

[1]Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA, USA; [2]Institute de Biologie, Nantes, France; [3]University of Salamanca, Salamanca, Spain; [4]Hospital Clinica, Barcelona, Spain; [5]MRT UAMS, Little Rock, Arkansas, USA; [6]DFCI, Boston, MA, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]Alexandria Hospital, Athens, Greece; [9]University of Gothenberg, Gothenberg, Sweden; [10]Rotterdam, The Netherlands; [11]Wilhelminenspital Der Stat Wien, Vienna, Austria; [12]Karolinska Institutet, Stockholm, Sweden; [13]Ankara University, Turkey; [14]Cancer Research and Biostatistics, Seattle, WA, USA; [15]Cross Cancer Institute, Canada; [16]University of Torino, Torino, Italy; [17]University of Malmo, Malmo, Sweden; [18]Royal Prince Alfred Hospital, Sydney, Australia; [19]St Vincent's Comprehensive Cancer Center, New York, NY, USA; [20]MD Anderson, Houston, TX, USA;

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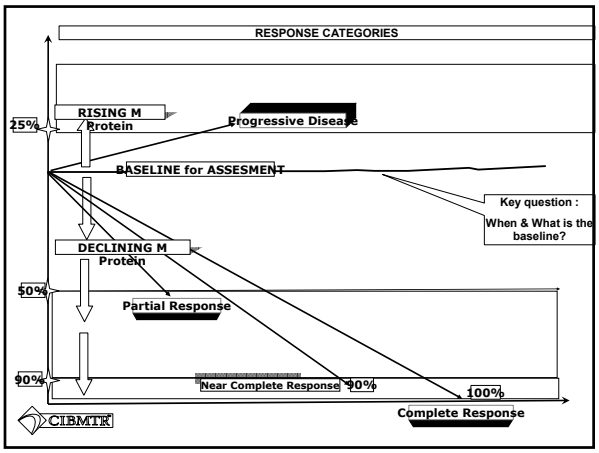

Major Changes in the new schema

Table 2 Summary of similarities and specific changes introduced to the New Uniform Response Criteria compared to the EBMT/IBMTR Criteria

- For patients with measurable levels of serum and urine monoclonal protein levels, the criteria for CR, PR and progressive disease remain unchanged. (Tables 5 and 6)
- Clarification and revision of important practical details of response evaluation (Table 4)
  - Elimination of mandatory 6 weeks wait time to confirm achievement of response
  - Introduction of a similar non-time-dependent confirmation for relapse and/or disease progression
  - Clarification of the "start time" for duration of response evaluation
  - Requirement of ≥PR as response requirement for new drug trials
  - Allow use of quantitative immunoglobulin levels in patients in whom the M-protein measurements are unavailable or unreliable
- Introduction of new response categories (Table 5) sCR and VGPR
  - Elimination of the minor response category
- Incorporation of response criteria for the serum FLC assay to enable assessment of response in patients with non- or oligo-secretory disease (Tables 5 and 6)
- Clarification that criteria for progressive disease (rather than criteria for "relapse from CR") are to be used for calculation of time to progression and progression-free survival in patients who are in CR. Criteria for relapse from CR are to be used only if DFS is calculated and reported
- Introduction of new category of clinical relapse or progressive disease (Table 6)
  - Introduces clinical relapse as a new optional end point

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- ➢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

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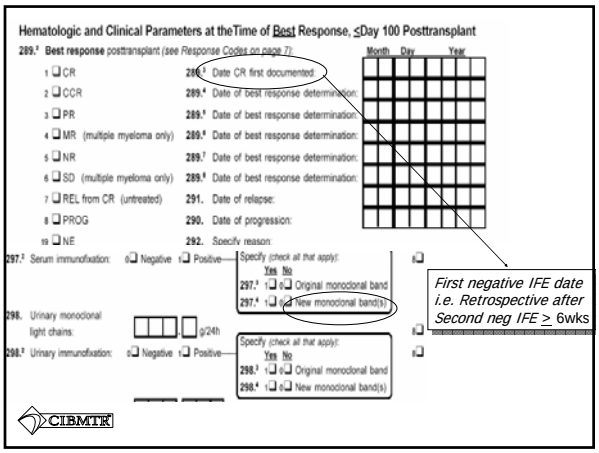

New vs. Old Criteria

- **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

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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 <u>at least one</u> of the following:
  1. Reappearance of serum or urine M-protein by immunofixation or eletrophoresis.
  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)

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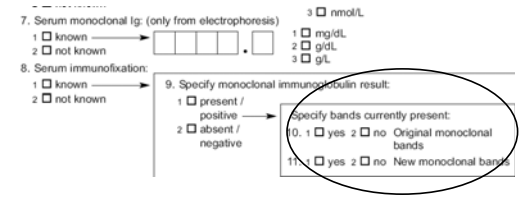
* To be used only if primary end point is DFS

Post Transplant Response



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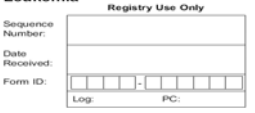
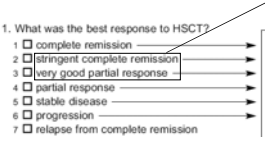
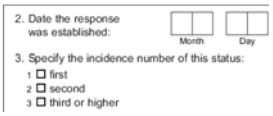
Post-Transplant Data Multiple Myeloma / Plasma Cell Leukemia



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





QUERIES:
Immunofixation not done → VGPR
Oligoclonal reconstituton is still CR
***Look at* original paraprotein !!!!**
"Too low to quantitate" - VGPR

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Oligoclonal Reconstitution

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

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Maintenance therapy

20. Was planned treatment per protocol (not for progressive disease) given post-HSCT?
1 ☐ yes → 2 ☐ no 3 ☐ unknown

Line of Therapy **1st Line of Therapy**
Systemic Therapy 21. 1 ☐ yes 2 ☐ no → cont. with q. 48
Number of cycles: 22. ☐☐ ☐ unknown / not applicable
Date started therapy: 23. ☐☐ Month ☐☐ Day ☐☐☐☐ Year
Date stopped therapy: 24. ☐☐ Month ☐☐ Day ☐☐☐☐ Year

- **Not for relapse or progression!**
- **Planned pre transplant**
- Interferon
- Prednisone
- Thalidomide
- Dexamethasone
- Revlimid (Lenalidomide)
- Velcade

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

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Post Transplant Form

Current Disease Status

99. What is the current status of the disease?
1 ☐ complete remission →
2 ☐ stringent complete remission →
3 ☐ very good partial response →
4 ☐ partial response →
5 ☐ stable disease →
6 ☐ progression →
7 ☐ relapse from complete remission

100. Date the response was established: ☐☐ Month ☐☐ Day

101. Specify the incidence number of this status:
1 ☐ first
2 ☐ second
3 ☐ third or higher

102. Plasma cells in bone marrow:
1 ☐ known → ☐☐ % →
2 ☐ not known

103. Plasma cell source:
1 ☐ aspirate
2 ☐ biopsy

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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 stem 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 – 5gm/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 NOT 1-0.6)
After Tx #2 → done 8 m from diagnosis
M spike – 0.1 g/dl (response is still 5 – 0.1 ie 98%)

Should we calculate Response to Tx#1 ?

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

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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 continuuing CR
    - PR → CR or continuuing PR
    - MR/SD → PR or CR or MR or SD

Thank You

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