Multiple Myeloma

How to Evaluate Response To Treatment and Relapse

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What is Multiple Myeloma?

Diagnostic Tools

Response to Treatment Evaluation

Progressive / Relapse Disease

Clinical Cases
What is Multiple Myeloma?

Multiple Myeloma Epidemiology
Progression from MGUS to Myeloma
Staging Systems (Salmon-Durie and ISS)
Physiopathology
Diagnostic Criteria
Features of Myeloma
Progression of Myeloma
Progression from MGUS to Myeloma

**GENOMIC INSTABILITY**
- Translocations at 14q32 50%
- Deletion of Chromosome 13 50%

**MICROENVIRONMENTAL CHANGES IN BONE MARROW**
- Increased Bone Resorption
- Increased Angiogenesis

**NORMAL CELL**
- Infection?
- Inflammation?

**MONOCLONAL GAMMAPATHY OF UNDETERMINED SIGNIFICANCE**
- N-RAS, K-RAS (30%)
- P16 Methylation (40%)
- Secondary translocations?

**MYELOMA**

*What is Multiple Myeloma?*
Monoclonal Gammopathy of Unknown Significance (MGUS)

- No clinical symptom
- Monoclonal peak < 3g/dL
- < 10% plasma cells in bone marrow
- No anemia, no hypercalcemia, no renal deficiency, no bone lesions

Progression to myeloma: 1% per year (+/-)
Definition

What is Multiple Myeloma?

Myeloma

Tumour plasma cells in the bone marrow ≥ 10%

A monoclonal immunoglobulin in the blood and/or urine
Physiopathology

What is Multiple Myeloma?

Lytic lesions
Pathologic fractures
Hypercalcemia

Bone destruction

Monoclonal antibodies

Urine: kidney failure
Tissue: neuropathy, amyloidosis

Anemia

Marrow infiltration

Reduced normal immunoglobulins

Infection

Multiple Myeloma
## Features of Myeloma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>May be raised</td>
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<tr>
<td>Renal disease</td>
<td>Up to 30% of patients at diagnosis</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Leukopenia &amp; thrombocytopenia unusual at diagnosis</td>
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<tr>
<td>Bone disease</td>
<td>Lytic lesions – pathological fractures</td>
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Other features include increased infections and extra-medullary disease.
What is Multiple Myeloma?

Plasmacytoma (extra medullary)

Plasmacytoma can be bone-related, extramedullary or solitary plasmacytoma

Non Secretory myeloma:
≥ 10% plasma cells in the bone marrow but no monoclonal protein neither heavy nor light chain (blood and urine)

Plasma Cell Leukemia

Plasma Cell Leukemia (primary or secondary)
• > 2000 plasma cells/mm³ or ≥ 20% plasma cells in WBC differential count

Peripheral Smear Report
• If reported, “Circulating Plasma Cells seen”, it does not necessarily means plasma cell leukemia: it depends on the number of circulating plasma cells
Progression of Myeloma

What is Multiple Myeloma?

1. Adapted from International Myeloma Foundation; 2001
Diagnostic Tools

Electrophoresis (SPEP and UPEP)
Serum and urine immunofixation
Bone marrow aspiration
To assess myeloma response, you need:

- Quantification of the serum monoclonal protein (+/- and the urines) (SPEP/UPEP and IFE)

- Serum Free light Chain quantification for light chain myeloma, kappa and lambda

- Bone marrow assessment if no more monoclonal protein detectable (cytology + flow cytometry)

- Imaging (MRI and PET) are currently evaluated
What is Monoclonal Immunoglobulin?
Serum Free Light Chain Assays - An Overview
Free light chain production by plasma cells

Kappa

Lambda
SPEP and Immunofixation (IFE)  
IgG λ Myeloma
SPEP and Immunofixation (IFE)
Lambda Light Chain Myeloma
Why is it difficult to evaluate myeloma?

- Criteria have changed over the time (due to improvement in treatment)

- New technologies developed (Flow cytometry, ASO-PCR, NGS)

- Raw data quality suboptimal (queries+++)

- Any evaluation requires two consecutive assessments (the six week interval between consecutive assessments is no longer required)
Response to Treatment Evaluation

EMBT Criteria
2006 IMWG Criteria
2011 IMWG Criteria
2006 IMWG Criteria
The Free Light Chain Test

1. Very useful for light chain myeloma
2. Necessary to define sCR

Be careful, sometimes it is the difference between the involved clonal light chain – the uninvolved but it can also be the ratio involved over uninvolved!

Normal polyclonal light chains: \( k = 3.3–19.4 \text{ mg/l}, \ l = 5.7–26.3 \text{ mg/l} \)
Normal polyclonal Free Light Chain (FLC) ratio \( k/l = 0.26-1.65 \)

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
IMWG implementation of the Free Light Chain Test for Light Chain Myeloma Evaluation

1. First assess response according to monoclonal proteinuria (>200 mg/d at least)

2. If proteinuria assessment not possible, use the serum Free Light Chain (FLC) test

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
### 2006 IMWG Criteria

<table>
<thead>
<tr>
<th>RESPONSE TO TREATMENT EVALUATION</th>
<th>CRITERIA FOR COMMON TYPE</th>
<th>LIGHT CHAIN if proteinuria assessment available (&gt; 200 mg/d at least)</th>
<th>LIGHT CHAIN if proteinuria assessment unavailable &gt; use the serum Free Light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response (PR)</td>
<td>Over 50% decrease of serum MP + 90% reduction in 24h urinary light chain excretion or proteinuria &lt; 200mg/d</td>
<td>&gt; 90% reduction in 24h urinary light chain excretion or proteinuria &lt; 200mg/d</td>
<td>50-89% decrease in the difference between involved and uninvolved FLC levels</td>
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<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>More than 90% decrease of Monoclonal Protein (MP) in the blood + Urine M protein &lt; 100 mg/d or SPEP/SPUP negative but IFs or IFu still positive</td>
<td></td>
<td>&gt; 90% decrease in the difference between involved and uninvolved FLC levels</td>
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<tr>
<td>Complete Response (CR)</td>
<td>No Monoclonal Protein (MP) in the blood + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
<td>Partial Response Criteria + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
<td>Serum and urine IF &lt; 0 and normal serum Free Light Chain ratio (0,26-1,65) and ≤ 5% plasma cells in bone marrow If FLC ratio not normal but individual K and L light chain values are normal: CR</td>
</tr>
<tr>
<td>Stringent (sCR)</td>
<td>CR and normal free light chain ratio and no clonal cells in bone marrow immunofluorescence or immunohistochemistry</td>
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Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
Progressive / Relapse Disease

Progressive disease
Clinical relapse
Relapse from CR
Progressive Disease (1):

25% increase compared to the lowest value of:

- Serum MP (absolute increase at least \( \geq 0.5 \text{ g/dl} \))
- Or: Urine MP (absolute increase at least \( > 200 \text{ mg/24h} \))
- Or: for patients without measurable urine MP, use the Serum Free Light Chain test: the difference between involved and uninvolved FLC levels (absolute increase at least \( >100 \text{ mg/L} \))
Progressive Disease (2):

- **Or:** Increase of $\geq 25\%$ bone marrow plasmocyte (absolute % at least $\geq 10\%$)
- **Or:** New bone lesion, plasmacytoma
- **Or:** Hypercalcemia ($> 2.65 \text{ mmol/L}$) attributed only to myeloma
Relapse from CR

1. Reappearance of serum or urine MP by IFE or SPEP/UPEP
2. Or ≥ 5% plasma cells in bone marrow
3. Or any other sign of progression (new plasmacytoma, lytic bone lesion, hypercalcemia)

All progressive/relapse categories require two consecutive assessments made at anytime
Clinical Cases
Baseline definition and lines of therapy
A patient has a M protein of 41 g/L at diagnosis and begins treatment with bortezomib plus lenalidomide and dexamethasone achieving a reduction in M protein to 2 g/L after 4 cycles. He then underwent a planned autologous transplant.
What is the baseline M protein value for assessing response to transplant?

A. At diagnosis
B. When collecting the stem cells
C. At transplantation
A patient has a M protein of 28 g/L at diagnosis. She completed therapy with lenalidomide and dexamethasone achieving a complete remission (M protein=0 and IFE negative in serum and urine plus bone marrow < 5%) and thereafter was place on lenalidomide maintenance. After 2 years on maintenance, her M spike rises to 24 g/L and she started bortezomib plus dexamethasone. After 4 cycles her M spike is now 6 g/L and she immediately proceeds to an autologous transplant with previously collect stem cells.
What is the baseline M protein value for assessing response to transplant?

A. 28 g/L  
B. 24 g/L  
C. 6 g/L
A patient has a M protein of 100 g/L at diagnosis. He is treated with the combination of bortezomib plus thalidomide plus dexamethasone and after 4 cycles his M spike is 60 g/L. He is switched to lenalidomide plus dexamethasone and he reached, after 4 additional cycles, a M spike of 5 g/L. Having reached a VGPR, he proceeds to ASCT followed by a short consolidation with lenalidomide plus dexamethasone three months after the transplantation. He is now in CR.
How many lines of treatment did the patient receive?

A. 1  
B. 2  
C. 3  
D. 4
Response evaluation
Common Difficulties

- First question: what is the baseline?
No baseline evaluation = not evaluable
Progression of disease or new line of treatment - usually means a new baseline
- If one data is missing for a defined category, you downgrade to the lower category
M-Protein = 0 and IF unknown = VGPR
M-Protein = 0 and IF=0 but no bone marrow evaluation = VGPR
- All response categories require two consecutive assessments made at anytime

- Check which criteria are used EBMT and/or IMWG?
Case N° 1

A patient is diagnosed with IgG kappa myeloma.

- M-spike = 60 g/L (from SPEP)
- 24-hr urine M-protein = 1000 mg
- Bone marrow biopsy had 40% plasma cells
- Patient was treated with bortezomib (Velcade®, Doxil® and Dexamethasone) for 4 cycles
The patient was re-evaluated after the 4th cycle of VDD. The M-spike = 24 g/L, proteinuria was 100mg/24hrs and there were 15% plasma cells on the bone marrow biopsy. The patient achieved a PR.

The patient received cytoxan for autologous stem cell mobilization. The next set of labs were obtained immediately prior to the start of the preparative regimen. The M-spike = 16 g/L, proteinuria was 100 mg/24hrs and 8% plasma cells were noted on the bone marrow biopsy.
What is the patient’s disease status immediately prior to the start of the preparative regimen?

A. Stable Disease (SD)
B. Very Good Partial Remission (VGPR)
C. Partial Remission (PR)
D. I do not know - not enough information provided to make determination
Case N° 1

The recipient from case #1 has had its ASCT. Lab studies are obtained at 60 and 100 days post HSCT.

- SPEP/UPEP are negative for an M-spike at Day 60 & 100
- Serum and Urine Immunofixation are positive for IgG kappa at Day 60 and 100
- Bone marrow biopsy < 5% plasma cells at Day 100
What disease response code would you report for this recipient at 100 days post-HSCT?

A. Partial Remission (PR)
B. Very Good Partial Remission (VGPR)
C. Complete Remission (CR)
D. None of the above

✓ B. Very Good Partial Remission (VGPR)
Case N° 2

A 55 year old male is diagnosed with IgG lambda myeloma. Results of the initial work-up include:

- Serum M-spike = 40 g/L
- 24-hr urine M-protein = 1000 mg
- Bone marrow biopsy = 60% plasma cells

Patient receives 2 cycles of lenalidomide (Revlimid®) and Dexamethasone and then re-evaluated

- Serum M-spike = 20 g/L
- 24-hr urine M-protein = 100 mg
What is the patient’s disease response after two cycles of Rev/Dex?

A. Partial Remission (PR)
B. Very Good Partial Remission (VGPR)
C. Stable Disease (SD)
The patient’s PR status was confirmed with a 2nd measurement. The patient received two additional cycles of Rev/Dex and was re-evaluated for disease response.

- Serum M-spike = 29 g/L
- 24-hr urine M-protein = 600 mg
- Bone marrow biopsy = 30% plasma cells
What is the patient’s disease response after a total of four cycles of Rev/Dex?

A. Stable Disease (SD)
B. Progressive Disease (PD)
C. Partial Remission (PR)

The correct answer is B. Progressive Disease (PD).
Patient is switched to Vincristine, Adriamycin and Decadron® (VAD) and is re-evaluated after two cycles.

- Serum M-spike = 14 g/L
- 24-hr urine M-protein = 150 mg
- Bone marrow biopsy = 15% plasma cells

The plan is to give IV Cytoxan mobilization. What is the patient’s disease response to the 2 cycles of VAD?
Case N° 2

A. Partial Remission (PR)
B. Very Good Partial Remission (VGPR)
C. Complete Remission (CR)
D. None of the above
The patient has achieved a PR after two cycles of VAD. What studies were used as a baseline to make that determination?

A. The studies obtained at diagnosis
B. The studies obtained at time of progression
C. The studies obtained after first two cycles of Rev/Dex

Correct answer: B.
Case N° 2

The patient underwent an ASCT and has been evaluated monthly for the 1st three months post HSCT.

Day +30 Evaluation

- Serum M-spike = 10 g/L
- Serum immunofixation (+) for IgG lambda
- 24-hr urine M-protein = 190 mg
- Bone marrow biopsy = 7% plasma cells
Case N° 2

Day +60 Evaluation

- SPEP/UPEP- no monoclonal band
- Serum/Urine immunofixation (+) for IgG lambda
- 24-hr urine for M-protein = 90 mg
Case N° 2

Day +100 Evaluation

- SPEP/UPEP- no monoclonal band
- Serum/Urine immunofixation (+) for IgG lambda
- 24-hr urine for M-protein = 90 mg
- Bone marrow biopsy < 5% plasma cells
Case N° 2

What is the best disease response to HSCT that you would report at Day +100 for this patient?

A. Stable Disease (SD)
B. Partial Remission (PR)
C. Very Good Partial Remission (VGPR)
D. Complete Remission (CR)

✓ C. Very Good Partial Remission (VGPR)
The patient received a planned maintenance therapy (Revlimid®) starting on Day 100 Post-ASCT. At 6 months of maintenance: ‘Best response to line of therapy’ needs to be answered.

What baseline studies would you use to determine the response he/she may have had to the Revlimid® maintenance?
Case N° 2

A. Use the results obtained prior to starting Revlimid®
B. Use the results obtained at diagnosis
C. Use the results obtained immediately prior to the start of the preparative regimen for HSCT
D. Use the results obtained at time of progression which is when VAD was initiated
A 75 year old man has lambda light chain myeloma. At diagnosis, his proteinuria is 5 g/24hrs and his serum lambda light chain is 1000 mg/L and kappa is 8 mg/L. At first assessment, you do not have access to his 24hrs proteinuria but his lambda light chain is 200 mg/L and kappa 9 mg/L.
Case N° 3

What is the proper response code to report at this first assessment?

A. Very Good Partial Remission (VGPR)
B. Partial Remission (PR)
C. Complete Remission (CR)
D. Stable Disease (SD)

Correct answer: A. Very Good Partial Remission (VGPR)
One month later, the serum lambda light chain is 10 mg/L and kappa is 15 mg/L. The K/L free light chain ratio is therefore 1.5. The proteinuria is 90 mg/24hrs. Serum and urine immunofixation are negative.
Case N° 3

What is the proper response code to report at this second assessment?

A. Very Good Partial Remission (VGPR)
B. Partial Remission (PR)
C. Complete Remission (CR)
D. Stable Disease (SD)

A. Very Good Partial Remission (VGPR)
Progression evaluation
A patient in third line is treated within a trial by the combination of bortezomib (Velcade®) + dexamethasone. The serum monoclonal nadir is 5g/L which is a partial response. He has a work-up every month. The latest measurement shows a serum M spike of 8 g/L.
What is the status?

A. Stable Disease (SD)
B. Partial Remission (PR)
C. Progression
Two months later, the monoclonal spike is 11 g/L. What is the status?

A. Stable Disease (SD)
B. Partial Remission (PR)
C. Progression
D. Progression but on hold until next evaluation
Case N° 1

One month after this last assessment, the monoclonal spike is 12 g/L. What is the status?

A. Stable Disease (SD)
B. Partial Remission (PR)
C. Progression
D. On hold until next evaluation
A patient has had a first line treatment with an ASCT followed by consolidation and one year maintenance. He keeps a small monoclonal spike of 3 g/L. Every three months, the M spike increases of 2 g/L. One year after maintenance, M spike reaches 11 g/L, and at two years after maintenance, M spike is 25 g/L. The physician decides to start a new line of treatment.
Case N° 2

When is the date of progression?

A. When M spike is 11 g/L
B. When M spike is 25 g/L
C. When a new line of treatment is initiated
D. On hold until next evaluation
Take home message

To evaluate response:

1/ What is the baseline and what are the lines of therapy?
2/ All the criteria must be met to define a response according to criteria
3/ Each status should be confirmed by second test giving consistent results

To evaluate progression:

1/ Progression can be biological and/or clinical
2/ Progression (biological) does not necessary mean start of a new treatment
3/ Each status should be confirmed by second test giving consistent results

When a second test confirms response/progression, the date of response/progression is the one defined by the first test
Conclusions

Make your own assessment and have it confirmed by your local principal investigator of the trial