Are We Integrating Biologic Advances in Multiple Myeloma Into Clinical Practice?

Minimal Residual Disease: A Measurable and Relevant Endpoint in Treatment

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MRD: A Measurable and Relevant Endpoint in Treatment

- Depth of response in Myeloma
  Are all CR the same

- What is MRD
  Techniques: NGF vs NGS
  Is it just about prolongation of PFS as a surrogate for OS

- Prognostic role of MRD
  MRD impacts OS

- MRD Rate and relevance in current treatment options and strategies
  MRD in NDMM
  MRD in RRMM
  MRD Including high risk MM

- Depth of MRD matters

- Work to do

- Conclusion
Treatment advances have increased the likelihood of achieving CR
The prognostic impact to CR comes from MRD

Multicentric, prospective study of 445 NDMM, post ASCT, 1/3 ≥ CR

147/295 NDMM (GEM2000) in CR post ASCT. MRD by MFC at day 100 after ASCT.

609 NDMM, GEM2000/GEM2005/GEM5010, MRD assessment 9 months after enrolment

Kapoor et al., JCO, 2010
Paiva et al., Blood, 2008
Lahuerta et al., JCO, 2017

Not reached vs 81 months

5-year OS rates 87% vs 59%

Not reached vs 59 months
Minimal Residual Disease, MRD

Diagnosis $10^{12}$

CR $10^{10}$

MRD

Negative MRD $< 10^6$

Immunophenotypic CR.
CMF (Sensibilité de $10^{-4}$ à $10^{-8}$ selon le nombre de couleurs (2 à 10 couleurs))

Molecular CR.
ASO-PCR (Se $10^{-5}$), NGS
MRD is about

Prolongs PFS as a surrogate for OS

Tumor dormancy, the ultimate objective for ‘cure’
Overall effect of MRD on OS

MRD-negative status was associated with significantly better OS overall (HR, 0.57; 95%CI, 0.46-0.71; P < .001)
MRD-negative status was associated with significantly better OS in CR patients (HR, 0.47; 95%CI, 0.33-0.67; \( P < 0.001 \))
IFM 2008

Phase 2. 31 NDMM, VRD x 3 - Transplant - VRD x 2 - Rev 1 year

<table>
<thead>
<tr>
<th></th>
<th>After induction</th>
<th>After ASCT</th>
<th>After consolidation</th>
<th>Completed Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n=31</td>
<td>n=31</td>
<td>n=31</td>
<td>n=31</td>
</tr>
<tr>
<td>Negative MRD</td>
<td>4/25 (16)</td>
<td>14/26 (54)</td>
<td>15/26 (58)</td>
<td>21/30 (70)</td>
</tr>
<tr>
<td>sCR + CR</td>
<td>7 (23)</td>
<td>14 (45)</td>
<td>15 (48)</td>
<td>18 (58)</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>18 (58)</td>
<td>21 (68)</td>
<td>26 (84)</td>
<td>26 (84)</td>
</tr>
</tbody>
</table>

MRD at $10^{-4}$-$10^{-5}$

Roussel et al. JCO 2014
Response-evaluable set. Assessed by next generation sequencing (NGS) in bone marrow.

Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.
POLLUX: MRD by Cytogenetic Risk Status ($10^{-5}$)

**In POLLUX, high-risk patients treated with daratumumab achieve MRD negativity and remain progression free**

**$P = 0.0009$.  ***$P = 0.0001$.**

Percentage of patients within a given risk group and treatment arm.

ClinicalTrials.gov Identifiers: NCT02136134

Weisel K et al., ASCO 2017
Depth of MRD matters

Phase 3 multicenter, IFM/DFCI 2009, NDMM

Randomize

- RVDx3
- CY (3g/m2) MOBILIZATION
  Goal: 5 x10⁶ cells/kg
- CY (3g/m2) MOBILIZATION
  Goal: 5 x10⁶ cells/kg
- Melphalan
  200mg/m²* + ASCT
- RVD x 2
- Revlimid 12 mos
- RVDx3
- CY (3g/m2) MOBILIZATION
  Goal: 5 x10⁶ cells/kg
- RVD x 5
- Revlimid 12 mos

MRD at post-maintenance

- P-value (trend): p<0.0001
- N at risk (events)

Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.
IFM 2009 trial

Role of treatment

![Graph showing the role of treatment with MRD assessment and patient status over time.]

- **Patients (%)**
  - negative MRD_RVD: 40, 39, 34, 31, 17, 1
  - negative MRD_Transp: 50, 47, 43, 38, 23, 4
  - positive MRD-RVD: 68, 62, 49, 35, 15, 1
  - positive MRD-Transplant: 66, 51, 38, 21, 11, 2

- **N at risk**
  - positive MRD-Transplant: 68, 62, 49, 35, 15, 1
  - positive MRD-RVD: 66, 51, 38, 21, 11, 2
  - negative MRD_Transp: 50, 47, 43, 38, 23, 4
  - negative MRD_RVD: 40, 39, 34, 31, 17, 1

*P < 0.001*
IFM 2009 trial

Role cytogenetics

![Graph showing the role of cytogenetics in IFM 2009 trial with data on patients and time since MRD assessment]
Work to do (1), MRD and – Clonal selection

Keats et al., Blood, 2012

Morgan et al., Oral communication
Work to do (2) MRD and – Best timing

Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.
Work to do (3) MRD and – MGUS like profile

Paiva et al., Leukemia, 2013
Work to do (4) MRD study

Various ways to study the BM, BM sampling, PET CT ….

Thal/dex followed by tandem ASCT

IFM 2009/DFCI - Imajem

Switch PET CT -

Switch PET CT +

p=0.000424
## Work to do (5) MRD and – treatment decision

<table>
<thead>
<tr>
<th>IFM 2018</th>
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<table>
<thead>
<tr>
<th>MRD1</th>
<th>MRD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD1</td>
<td>MRD2</td>
</tr>
</tbody>
</table>

### Standard Risk

- **PI**+**ImidsD-MoAB** x6

<table>
<thead>
<tr>
<th>MRD1</th>
<th>MRD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDT1 + PI+ImidsD-MoAB x4</td>
<td>R</td>
</tr>
<tr>
<td>PI+ImidsD-MoAB x7</td>
<td>Maint A</td>
</tr>
<tr>
<td>Maint B</td>
<td></td>
</tr>
</tbody>
</table>

### High Risk

- **PI**+**ImidsD-MoAB** x6

<table>
<thead>
<tr>
<th>MRD1</th>
<th>MRD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDT1 + PI+ImidsD-MoAB x6</td>
<td>HDT2</td>
</tr>
<tr>
<td>Maint C</td>
<td></td>
</tr>
<tr>
<td>Maint D</td>
<td></td>
</tr>
<tr>
<td>Maint A</td>
<td></td>
</tr>
<tr>
<td>Maint B</td>
<td></td>
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</table>

### Work to do (5)

- **MRD** and – treatment decision
Minimal Residual Disease Assessment: Not Relevant for Clinical Practice Yet

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine
There are patients with old drugs and old tests that do well.

Functional cure?

Martinez-Lopez et al, Blood 2011
Impact of MRD: Meta-analysis
Are these the same patients?

Getting to **Minimal Residual Disease (MRD)**: New Definitions for CR

- **S.S. Patient**
  - CR
  - Stringent CR
  - Flow CR
  - NGS CR
  - Antibodies Genomic Based Tx

- **MRD**
  - 1 × 10^12
  - Newly diagnosed

- **Disease burden**
  - Newly diagnosed 1 × 10^12
  - CR
  - Stringent CR
  - Flow CR
  - NGS CR
  - Antibodies Genomic Based Tx

- **Newly diagnosed**
How you measure MRD impacts the results

**MRD at pre-maintenance**

- **P-value (trend):** $p<0.0001$

**MRD at post-maintenance**

- **P-value (trend):** $p<0.0001$

Avet-Loiseau et al, ASH 2015
MRD testing is not a surrogate for Cure

Lahuerta et al, JCO 2017
MRC Myeloma IX: PFS and OS Do Not Plateau

- MRD negativity at Day 100 post-ASCT was associated with improved PFS (P<0.0001) and OS (P=0.0183)

### PFS

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>MRD–</th>
<th>MRD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>145</td>
<td>59</td>
</tr>
<tr>
<td>24</td>
<td>107</td>
<td>42</td>
</tr>
<tr>
<td>36</td>
<td>73</td>
<td>24</td>
</tr>
<tr>
<td>48</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>60</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>72</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS: MRD– 28.6 months, MRD+ 15.5 months

### OS

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>MRD–</th>
<th>MRD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>237</td>
<td>132</td>
</tr>
<tr>
<td>12</td>
<td>220</td>
<td>124</td>
</tr>
<tr>
<td>24</td>
<td>197</td>
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<td>36</td>
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<td>48</td>
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<tr>
<td>60</td>
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<td>0</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>84</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Median OS: MRD– 80.6 months, MRD+ 59.0 months

Numbers at risk:
- MRD–: 200, 145, 107, 73, 41
- MRD+: 87, 59, 42, 24, 14

Cannot use MRD to decide who gets a transplant

2/3 of these patients were from HDT, 1/3 from delayed HDT

Avet-Loiseau et al, ASH 2015
MRD changes post transplant do not impact OS

Lahuerta et al, JCO 2017
Conclusion

YES. Minimal Residual Disease is
A Measurable and Relevant Endpoint in Treatment

➢ Is manageable in most countries
➢ Has demonstrated a prognostic role, PFS and OS
➢ You already have implemented depth of response in your practice for treatment decision
  - You decide a treatment strategy based on known depth of response
  - You optimize a treatment scheme to improve depth of response, ASCT, consolidation, maintenance...
➢ Time for the next step, MRD-based treatment choice decision making
Summary (Fallacies) of MRD testing

- MRD is a surrogate for cure
- If you are MRD negative, you can stop treatment
- If you are MRD positive after transplant, you need to change from standard treatment
- MRD is the only predictor of good long term outcomes
- If you convert from MRD negative to MRD positive, you need to change therapy
- MRD assessment in the marrow is enough to declare victory
What can MRD testing be used for

- Comparing across clinical trials
- Assessing efficacy of new treatment approaches
- Prognosis

But **not** for current clinical decision making

There are too many unknowns that will be addressed by ongoing trials
Never give up!

Thank you for your attention