Minimal residual disease in myeloma – opportunities and controversies

Dr Roger Owen

Consultant Haematologist
St James’s Institute of Oncology
It’s the depth of response, stupid........

It’s the economy, stupid........
Why do we need MRD?

- Complex multicomponent therapy
- M protein issues
- Increasing survival
CR rates are increasing

Stringent CR?


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Survival regarding every component of sCR definition.

IHC is not sensitive enough to detect low MRD levels

5% of the patients in conventionally-defined CR had BM clonality according to IHC criteria

The majority of $\kappa/\lambda$ ratios after chemotherapy are polyclonal *, and clonality can only be detected after identification of phenotypically aberrant cells

* BM clonality is defined when the $\kappa/\lambda$ ratio is $>4:1$ or $<1:2$ for $\kappa$ and $\lambda$ patients, respectively, after counting $\geq 100$ PCs

Trainspotting
Detection of clonal immunoglobulin gene rearrangements in the peripheral blood progenitor cells of patients with multiple myeloma: the potential role of purging with CD34 positive selection


British Journal of Haematology, 1997, 97, 46–55

Circulating plasma cells in multiple myeloma: characterization and correlation with disease stage


Received 4 October 1996; accepted for publication 18 December 1996

Flow cytometric disease monitoring in multiple myeloma: the relationship between normal and neoplastic plasma cells predicts outcome after transplantation


blood

2002!
MRD: What do we need?

- Applicability
- Quantitative methodology
- Predicts PFS and OS including CR pts
- Cytogenetic risk groups
- Transplant eligible and ineligible
- Upfront and relapse
- Independent of treatment
Minimal Residual Disease Assessed by Multiparameter Flow Cytometry in Multiple Myeloma: Impact on Outcome in the Medical Research Council Myeloma IX Study


Myeloma Academy ROADSHOW
Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma

Joaquin Martínez-Lopez,1 Juan J. Lahuerta,1 François Pepin,2 Marcos González,3 Santiago Barrio,1 Rosa Ayala,1 Noemí Puig,3 María A. Montalban,1 Bruno Paiva,4 Li Weng,2 Cristina Jiménez,3 María Sopena,1 Martin Moorhead,2 Teresa Cedena,1 Immaculada Rapado,1 María Victoria Mateos,3 Laura Rosiñol,5 Albert Oriol,5 María J. Blanchard,7 Rafael Martínez,8 Joan Bladé,5 Jesús San Miquel,4 Malek Faham,2 and Ramón García-Sanz3
## Comparison of methods

<table>
<thead>
<tr>
<th></th>
<th>Flow cytometry</th>
<th>ASO-PCR</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability</td>
<td>&gt;95%</td>
<td>60%</td>
<td>~90%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>10^{-4}/10^{-5}</td>
<td>10^{-5}</td>
<td>10^{-5}/10^{-6}</td>
</tr>
<tr>
<td>False positive</td>
<td>No</td>
<td>Potentially</td>
<td>Potentially</td>
</tr>
<tr>
<td>False negative</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Baseline sample</td>
<td>Desirable</td>
<td>Essential</td>
<td>Essential</td>
</tr>
<tr>
<td>Quality assessment</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Turnaround times</td>
<td>Short</td>
<td>High</td>
<td>?Medium</td>
</tr>
<tr>
<td>Quantitative</td>
<td>Direct</td>
<td>Yes</td>
<td>Yes, but......</td>
</tr>
</tbody>
</table>
Effect of MRD according to cytogenetic risk profile

A

![Graph showing Progression-Free Survival](image)

- Adverse; MRD+
- Adverse; MRD-
- Favorable; MRD+
- Favorable; MRD-

$\chi^2 = 68.4949$

$P < .001$

B

![Graph showing Overall Survival](image)

- Adverse; MRD+
- Adverse; MRD-
- Favorable; MRD+
- Favorable; MRD-

$\chi^2 = 40.1305$

$P < .001$
Transplant ineligible – Myeloma XI

Log-Rank
$\chi^2_1 = 15.5105$
$P < 0.0001$
HR: 0.38 95% CI (0.23, 0.63)

1: MRD+
2: MRD−

Months since randomisation
What about salvage Rx?

Ashcroft et al (2013) ASH Abstract
Impact of therapy received

\[ \chi^2 = 24.30 \]
\[ P < .00001 \]

CR patients only?
The effect of MRD status on PFS (CR patients)

$$\chi^2\text{ (adjusted)} = 35.85; \quad P < 0.0001$$

<table>
<thead>
<tr>
<th>CR patients</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative</td>
<td>60 months</td>
</tr>
<tr>
<td>MRD-positive</td>
<td>36 months</td>
</tr>
</tbody>
</table>

No. of patients at risk
- MRD-negative: 362, 359, 301, 211, 155, 96, 65, 35, 16, 12, 1
- MRD-positive: 134, 129, 86, 51, 33, 19, 12, 7, 7, 5, 0

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- 3-year PFS: 72% MRD-negative versus 50% MRD-positive patients
- 5-year PFS: 50% MRD-negative versus 29% MRD-positive patients
- Majority of MRD-positive patients progressed by 6 years, whereas nearly 50% of MRD-negative patients remained progression-free

CR, complete response; MRD, minimal residual disease; PFS, progression-free survival.
The effect of MRD status on OS (CR patients)

\[ \chi^2 \text{ (adjusted)} = 15.06; \quad P < 0.0001 \]

No. of patients at risk:

- MRD-negative: 362, 359, 331, 274, 218, 138, 76, 34, 8, 3, 1
- MRD-positive: 134, 131, 111, 81, 55, 35, 20, 10, 5, 5, 2

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- 3-year OS: 93% MRD-negative versus 79% MRD-positive patients
- 5-year OS: 78% MRD-negative versus 60% MRD-positive patients

CR patients | Median OS
---|---
MRD-negative | NR
MRD-positive | 82 months

Myeloma Academy ROADSHOW  CR, complete response; MRD, minimal residual disease; NR, not reached; OS, overall survival.
## MRD and paraprotein response

<table>
<thead>
<tr>
<th>Response post-ASCT</th>
<th>MRD level at day 100 post ASCT – number (percentage) of patients achieving specified MRD range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>CR</td>
<td>183 (86)</td>
</tr>
<tr>
<td>VGPR</td>
<td>34 (47)</td>
</tr>
<tr>
<td>PR</td>
<td>24 (28)</td>
</tr>
<tr>
<td>MR</td>
<td>1 (13)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (13)</td>
</tr>
<tr>
<td>UTD</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
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</table>
MRD and M protein response

## Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS Univariate</th>
<th>PFS Multivariate</th>
<th>OS Univariate</th>
<th>OS Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>p-value</td>
<td>$\chi^2$</td>
<td>p-value</td>
</tr>
<tr>
<td>Log(MRD)</td>
<td>33.0</td>
<td>&lt;.0001</td>
<td>19.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Response post ASCT^</td>
<td>20.5</td>
<td>&lt;.0001</td>
<td>1.3</td>
<td>.25</td>
</tr>
<tr>
<td>International Staging System (1-3)</td>
<td>4.5</td>
<td>.03</td>
<td>.72</td>
<td>.40</td>
</tr>
<tr>
<td>Cytogenetics†</td>
<td>39.8</td>
<td>&lt;.0001</td>
<td>41.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Log(β2 microglobulin)</td>
<td>8.3</td>
<td>.004</td>
<td>1.8</td>
<td>.18</td>
</tr>
<tr>
<td>Platelets*</td>
<td>10.6</td>
<td>.001</td>
<td>3.8</td>
<td>.05</td>
</tr>
<tr>
<td>Haemoglobin**</td>
<td>15.0</td>
<td>.0001</td>
<td>7.5</td>
<td>.006</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>.1</td>
<td>.75</td>
<td>.01</td>
<td>.92</td>
</tr>
<tr>
<td>Gender</td>
<td>.3</td>
<td>.58</td>
<td>.23</td>
<td>.63</td>
</tr>
</tbody>
</table>

WHAT'S NEXT?
FDA-NCI Roundtable: Symposium on Flow Cytometry Detection of Minimal Residual Disease in Multiple Myeloma, March 24, 2014

On March 24, 2014, an FDA-NCI roundtable symposium on minimal residual disease (MRD) detection in multiple myeloma (MM) was held at the FDA in Silver Spring, Maryland. The goal of this meeting was twofold: (1) to examine the evidence on the clinical utility of MRD in MM as a biomarker for drug response; and (2) to ascertain the status of consensus concerning the standardization of a flow cytometric device (assay), as well as its relationship to molecular tests, for the detection of MRD in MM. Over the past few years, three previous FDA workshops have been held to address MRD detection in acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML). While the role of MRD is well-established in these three hematological malignancies, its role in regulatory decisions within the agency remains in the realm of ongoing policy development.
LYMPHOID NEOPLASIA

Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction

Andy C. Rawstron,1 Walter M. Gregory,2 Ruth M. de Tute,1 Faith E. Davies,3 Sue E. Bell,2 Mark T. Drayson,4 Gordon Cook,1 Graham H. Jackson,5 Gareth J. Morgan,3 J. Anthony Child,2 and Roger G. Owen1

OS BY MRD VALUE

EXCLUDING MRD ≥ 10%:
$X^2 (TREND) = 7.41$ $X^2 (TREND) = 12.36$

P = .0005 P = .0004
Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma

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Outcome determined by level of disease not treatment received

MRD: Comparison of induction regimens

<table>
<thead>
<tr>
<th></th>
<th>CVAD</th>
<th>CTD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post induction</td>
<td>13%</td>
<td>25%</td>
<td>P=0.004</td>
</tr>
<tr>
<td>(n=252)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 100</td>
<td>54%</td>
<td>71%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>(n=397)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing flow-CR rates after induction and HDT/ASCT for different regimens](image)
Maintenance

```
No. at risk
NM; MRD+   53  28  18  12  8  5  4  0
NM; MRD−   93  73  50  34  25  15  8  1  0
T; MRD+    53  40  30  22  13  7  2  0
T; MRD−    93  78  60  48  29  20 10  1  0

\chi^2 = 18.6153
P < .001
```

Progression-Free Survival
(proportion)

Time Since MRD Assessment (months)
No change in conventional response with thalidomide maintenance but clear differences in neoplastic plasma cell levels

• “Using electrophoresis and immunofixation as a monitoring technique, there was no difference between the thalidomide maintenance and no maintenance arms in the percentage of patients that upgraded response status over time (P .19).” (1)

Combined cytogenetics plus MRD monitoring after HDT/ASCT identifies CR patients with early relapses and dismal survival

**Time to progression (%)**
- Median: 7y
- Median: 2y
- Median: 0.5y

**Overall survival (%)**
- Median: NR
- Median: 4y
- Median: 2y

\[ P < .001 \]

* \( t(4;14), t(14;16) \) and/or del(17p) \)

GEM2000 & GEM2005MENOS65 studies

**Standard-risk FISH + MRD negative**
**High-risk* FISH OR MRD positive**
**High-risk* FISH + MRD positive**

Long-term results of the GIMEMA VEL-03-096 trial in MM patients receiving VTD consolidation after ASCT: MRD kinetics' impact on survival

S Ferrero1,4, M Ladelto1,4, D Drandi1, F Cavallo1,2, E Genuardi1, M Urbano1, S Caltagirone1, M Grasso2, F Rossini2, T Guglielmelli2, C Cangialosi2, AM Liberati2, V Callea3, T Carovita2, C Crippa2, L De Rosa2, F Pisani2, AP Falcone2, P Pregno2, S Oliva1,2, C Terragna3, P Musto3, R Passera3, M Boccadoro1,2 and A Palumbo1,2

Polymerase chain reaction (PCR)-based minimal residual disease (MRD) analysis is a useful prognostic tool in multiple myeloma (MM), although its long-term impact still needs to be addressed. This report presents the updated results of the GIMEMA-VEL-03-096 trial. Thirty-nine MM patients receiving bortezomib–thalidomide–dexamethasone after autologous transplantation were monitored for MRD by both nested and real-time quantitative-PCR until relapse. Our data confirm the strong impact of MRD on survival: overall survival was 72% at 8 years median follow-up for patients in major MRD response versus 48% for those experiencing MRD persistence (P=0.041). In addition, MRD kinetics resulted predictive for relapse: indeed median remission duration was not reached for patients in major MRD response, 38 months for those experiencing MRD reappearance and 9 months for patients with MRD persistence (P = 0.001). Moreover, (1) 36 patients achieving major MRD response (67%) benefit of excellent disease control (median TNT: 42 months); (2) MRD reappearance heralds relapse, with a TNT comparable to that of MRD persistence (9 versus 10 months, P = 0.706); (3) the median lag between MRD reappearance and need for salvage treatment is 9 months. These results suggest the usefulness of a long-term MRD monitoring in MM patients and the need for maintenance or pre-emptive treatments ensuring durable responses.

Leukemia (2015) 29, 689–695; doi:10.1038/leu.2014.219
Outcome prediction in SPB

IMWG – “solitary plasmacytoma with minimal marrow involvement”

The future

- Role of imaging
- Need for minimum sensitivity of 10-5
- Use of monoclonal antibodies
- MRD-genomics
MRD: What do we need?

- Applicability ✓
- Quantitative methodology ✓
- Predicts PFS and OS including CR pts ✓
- Cytogenetic risk groups ✓
- Transplant eligible and ineligible ✓
- Upfront and relapse ✓
- Independent of treatment ✓
Myeloma Academy ROADSHOW

Can regular survival point for PMI and show us how?

Yes We Can!

All Posters

Myeloma UK