Multiple Myeloma – Pathophysiology and Epidemiology

Multiple myeloma (MM) is a B-cell malignancy in which abnormal, clonal plasma cells proliferate and accumulate in the bone marrow. These abnormal cells, referred to as myeloma cells, disrupt normal bone marrow function and invade bone. Myeloma cells produce and secrete significant quantities of monoclonal protein (M-protein) into the blood and/or urine.\(^1\) The clinical features of MM include hypercalcemia, renal failure, anemia, osteolytic bone lesions, and increased susceptibility to infections.\(^2\)

Nearly all MM cases are preceded by an asymptomatic, pre-malignant condition known as monoclonal gammopathy of undetermined significance (MGUS) which may progress to a smoldering MM phase.\(^3\)

The disease course to symptomatic MM is driven by multiple genomic events within myeloma cells and abnormal interactions between myeloma cells and the bone marrow microenvironment.\(^2\) Several chromosomal abnormalities have been identified in patients with MM and involve translocations, deletions, or amplifications.\(^3\)

- MM is the second most common hematologic malignancy and accounts for approximately 13% of all hematologic cancers.\(^4\)
- Globally, an estimated 114,000 new cases of MM are diagnosed annually, with 80,000 deaths per year attributable to the disease.\(^4\)
- MM predominantly affects elderly people, and is most frequently diagnosed between the ages of 65–74 years. MM is more common in males and African Americans compared to females and Caucasians, respectively.\(^3\)
- Overall, the 5-year survival among adults with MM is 48.5%.\(^3\)

Complete Response Categories in MM

Improvements in therapeutic agents and regimens have driven the evolution of the International Myeloma Working Group (IMWG) response criteria to include deeper measures of response. The definition of a complete response (CR) was first introduced in 1998 and further refined in 2006 to include stringent CR.\(^5,6\) Additional clarifications to CR were introduced in 2011 to include molecular and immunophenotypic CR (not shown).\(^8\) Recently, the IMWG included measures of minimal residual disease (MRD) assessments.\(^8\)

- CR*: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <3% plasma cells in bone marrow aspirates.
- sCR*: CR plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 1.0 or ≥ 1.0 for κ and λ patients, respectively, after counting ≥ 100 plasma cells).
- MRD-negative\(^7\): Absence of aberrant clonal plasma cells on bone marrow aspirate, ruled out by an assay\(^9\) with a minimum sensitivity of 1 in 10\(^5\) nucleated cells or higher (i.e. 10\(^4\) sensitivity).
- Imaging-positive MRD-negative\(^7\): MRD negativity as defined by NGF or NGS plus disappearance of any area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.
- Sustained MRD-negative\(^7\): MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined above, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).

Minimal Residual Disease – Why Assess It?

The treatment of MM has improved significantly over the last decade, resulting in many patients exhibiting a CR to front-line therapy.\(^10\) Unfortunately, the disease course of MM is characterized by a pattern of recurrent remissions and relapses.\(^11\) Even after an initial CR, many patients inevitably relapse and MM remains an incurable disease.\(^10\)

While standardization and consensus on the role of MRD testing in MM is ongoing, the risk of relapse has shown to be correlated to MRD undetectable by conventional techniques. MRD refers to the persistence of small numbers of myeloma cells that remain after therapy and contribute to relapse and disease progression.\(^8,11\) In recent years, increasingly sensitive assays to detect MRD have been developed.\(^12\)

In a retrospective analysis of 3 clinical trials, 40% of patients with MM relapsed within 4 years after achieving a CR\(^13\)

Hypothetical Correlation on Depth of Response and Risk of Relapse
When is MRD Assessment Performed?
The 2016 IMWG criteria recommends testing MRD status when patients achieve a CR.² MRD tests have also been initiated throughout the treatment continuum (e.g. after induction, high-dose therapy/autologous stem cell transplant, consolidation, maintenance) to monitor the course of disease.² ⁹ ¹³ ¹⁴ ¹⁵

Features of MRD Detection Methods ⁹ ¹² ¹³

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<th>Method</th>
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| MFC (≥ 8-color) | Differentiates between normal and abnormal plasma cells through detection of cell-surface marker expression | ~100%         | 10⁻⁶–10⁻¹²  | • Widely applicable and available
• Hours
• Relatively inexpensive
• Clonal heterogeneity undetectable
• Standardized by the EuroFlow consortium
• Requires bone marrow aspirate
• Fresh sample necessary
• Does not require baseline sample |
| ASO–PCR        | Analysis of VDJ heavy chain regions for detection of myeloma specific Ig rearrangements | 60%–70%       | 10⁻⁴–10⁻⁶  | • Intermediate applicability and availability
• Days to weeks
• More expensive
• Clonal heterogeneity undetectable
• Standardized (EuroMRD)
• Requires bone marrow aspirate
• Patient-specific primers necessary
• Requires baseline sample |
| NGS            | Use of high throughput sequencing to detect clonal Ig VDJ gene rearrangements | ~90%          | 10⁻⁶        | • Limited availability
• One week or more
• Expensive, but costs decreasing
• Limited clonal heterogeneity detected
• Not yet standardized
• Bone marrow aspirate or peripheral blood sample acceptable
• Fresh sample not necessary
• Requires baseline sample or stored sample from a time point with detectable disease |
| PET/CT         | Permits detection of lesions demonstrating metabolic activity together with morphologic information and has advantage of detecting extramedulary disease | ~100% Variable sensitivity |                      | • Intermediate availability
• Hours
• Expensive
• Detects extramedullary disease
• False-negative and false-positive results with coexisting infection or inflammation |

MRD: minimal residual disease; MFC: Multiparametric flow cytometry; ASO: Allele-specific oligonucleotide; PCR: polymerase chain reaction; NGS: Next-generation sequencing; PET: positron emission tomography; CT: computed tomography

MRD in MM Summary
Relapses in MM could potentially reflect the presence of residual disease. Recombinant advances in molecular testing using MFC, ASO–PCR, and NGS, and imaging techniques such as PET/CT, have enabled the detection of myeloma cells with greater sensitivity.¹¹ ¹³

Ongoing studies will continue to define what level of MRD may be clinically relevant and how MRD assessment may inform treatment decision-making.³ Additionally, an understanding of the heterogeneity of the disease biology may also be important in predicting the risk of relapse and sustainability of a response. Some patients who present with high-risk features at baseline may have persistent MRD despite achieving a CR, while patients with MGUS-like gene expression may experience better outcomes independent of CR status.⁵

Currently, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) do not consider MRD a regulatory surrogate clinical endpoint. Additional clinical trials are needed that incorporate MRD testing in MM and may further validate the relationship of sustained MRD-negativity and improved outcomes.¹⁶

References