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Editorial

Minimal Residual Disease Assessment in Multiple Myeloma is A Major Challenge in Clinical Practice

Nahla A M Hamed*

Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt

Abbreviation

MRD: Minimal Residual Disease; NGS: Next Generation Sequencing; MFC: Multiparameter Flow Cytometry; NGF: Next-Generation Flow Cytometry; ASO-qPCR: Allele Specific Oligonucleotide Quantitative Polymerase Chain Reaction; TTP: Time to Progression; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; miRAMM: Monoclonal Immunoglobulin Rapid Accurate Mass Measurement; CTCs: Circulating Tumor Cells.

Abstract

Current treatment approaches of myeloma are now sufficiently effective that high-sensitivity quantitative MRD analysis is required for meaningful response measurement, particularly in large multicenter trials. However, its implementation is hampered by differences in the assays and analytical methods employed between different routine laboratories. The sensitivity and specificity of traditional techniques for MRD assessment can be improved in the future. This article aims at providing a comprehensive summary of the latest MRD knowledge in the field of myeloma, and to outline future directions.

Introduction

Myeloma patients in CR had detectable residual disease levels across 4 or more logs [1]. Improved therapies eradicate the dominant clone, while resistant sub-clones persist and remain undetectable. Characterization of these resistant clones and designing therapies against them move us closer to cure MM [2]. Concepts such as "depth of response," "minimal residual disease (MRD)," and "surrogate survival markers" have become the subject of extensive research in MM [3]. The role of MRD in MM is still a matter of extensive debate [4]. MRD quantitation may be more informative than MRD status [5]. Quantitative MRD detection is possible at 10^{-5} by flow cytometry and 10^{-6} by high throughput sequencing [1]. The ideal cut-off for the definition of MRD negativity might be 10^{-6} [6].

Minimal Residual Disease Assessment in Myeloma

Current Techniques for MRD Detection

Multiparameter flow cytometry (MFC) including next-generation flow cytometry (NGF), using 8 color combinations [7], next-generation sequencing (NGS), and allele specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR) are validated sensitive assays to quantitatively assess MRD [2]. MFC is a cellular technique [2] that has widespread availability, improving sensitivity, improved standardization, lower cost, and rapid processing time [2]. The sensitivity of modern MFC-based MRD monitoring has been boosted into that achieved on molecular grounds ($\leq 10^{-5}$) due to the availability of ≥8-color digital flow cytometers coupled to novel sample preparation protocols that allow fast and cost-effective routine evaluation of >5 million nucleated cells [4]. MFC results critically depend on bone marrow aspiration quality. False negative results should be interpreted with caution since myeloma cells are underrepresented in bone marrow aspirates. Plasma cells are fragile and myeloma cells are less resilient and die rapidly when removed from the bone marrow. Hemodilution and sampling error can also cause false negative results [2]. QASO-PCR and NGS are molecular

***Corresponding Author:** Nahla AM Hamed, Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt, E-mail: drhamedn@hotmail.com

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techniques that measures the patient-specific clonal rearrangements of the Ig gene [6] .qASO-PCR and NGS have a sensitivity of $<10^{-4}$–10^{-6} [6]. ASO-qPCR has higher sensitivity and use banked samples [2]. qASO-PCR and NGS have restricted applicability [6] attributed to variable levels of primer annealing with unpredictable amplification/quantitation results due to the high number of somatic hyper mutations [8]. ASO-qPCR has the limitation of requiring patient specific probes which is not required by NGS [2]. The laboratory assay of MRD represents a challenge in the case of monoclonal antibodies therapy as low levels of antibody can lead to false-positive results. The use of NGS is not affected by antibody-based treatment. Other therapies including chimeric antigen receptor T cells may require other strategy yet to be defined [7].

Imaging Techniques for the Assessment of MRD (PET-CT and MRI)

Fluorodeoxyglucose-positron emission tomography (PET) imaging has prognostic significance and would represent the most effective imaging tool to monitor MRD in MM [9]. A specific advantage of PET imaging is its ability to detect extra medullary disease which is present in up to 10% of patients at diagnosis and at a high proportion at the time of relapse [7] and represents an adverse prognostic event [9]. PET/CT can also detect focal areas of bone marrow infiltration by myeloma cells which may be missed by performing blind bone marrow biopsy [2]. MRI is the most sensitive noninvasive imaging technique for providing relevant information on spine bone involvement, the extent and nature of soft tissue disease and the pattern of marrow infiltration (normal, focal, heterogeneous, or diffuse). However, MRI does not properly identify myeloma active lesions after treatment. Focal lesions may remain hyperintense in both responding and non-responding patients for several months after therapy due to treatment-induced necrosis and inflammation [9]. The role of the newer imaging technique PET-MRI in myeloma is under investigation [2].

The Timing of MRD Monitoring

The timing of MRD testing depends on the type of treatment and the patient eligibility for transplant. Measurement of MRD should be conducted after each treatment stage.

a) Non-eligible to transplant: MRD testing should be done at the time a patient is expected to have the most optimal response following induction treatment [7].

b) Transplant eligible: The typical timing for MRD assessment should be done at the time when a patient achieves the most optimal response following induction treatment, and at day +100 after autologous stem cell transplant [2].

Maintenance treatment

MRD testing should be conducted before the start of maintenance and at subsequent time points (e.g. every 6 months) [7]. Examining serial MRD measurements may be a useful approach to detect the trajectory of disease before clinical relapse [2].

MRD Negativity

Cut-off for the MRD negativity is of utmost importance in order to define rules for stopping treatment (during maintenance for example), or to introduce the concept of cure [10]. Undetectable (also referred as negative) MRD implies that less than 1 in 10^{-5} residual tumor cells are detected in the bone marrow following treatment [7]. Sustained MRD negativity was proposed by the IWMG consensus as the confirmation of NGS/NGF and PET negativity a minimum of one year apart [10]. Not all patients are negative with both techniques due to the heterogeneous nature of skeletal involvement in the disease. Patients may be MRD negative by flow cytometry and still positive on PET-CTs. MRD flow represents only sampling from the pelvic bone, it will not detect active disease in other areas of involvement (vertebral bones, skull, long bones, etc.). Therefore, PET-CTs are becoming more important [11]. Most patients who achieve MRD-negative status eventually relapse [9]. The definition of "loss of MRD-negative status" needs clarification, as it will impact the new definition of disease-free survival [10].

Potential Applications of MRD Assessment

MRD could be used as a biomarker to evaluate treatment efficacy, and help on therapeutic decisions [4]. MRD testing offers a unique opportunity to identify effective drugs early, to stop ineffective drugs early in their development cycle and to give patients rapid access to new efficacious drugs [12].The prognostic value of MRD is independent of treatment type, with patients achieving less than 0.01% residual disease have the same outcome whether they received CVAD or CTD induction. [1]. MRD monitoring is suggested to be clinically relevant also in elderly patients. [4]. However, MRD-negative elderly cases did not experience the same outcome after two different regimens (VMP and VTP). This finding suggests that the level of MRD tumor depletion may be different between the two regimens [4]. In general, escalation or de-escalation of therapy based on MRD assay results is not yet recommended [11]. MRD negativity is a strong predictor of clinical outcomes. MRD negativity (versus positivity) was associated with better PFS and may act as surrogate for overall survival [13]. Patients with high ($<10^{-3}$), intermediate (10^{-3} to 10^{-5}), and low ($>10^{-5}$) MRD levels showed significantly different TTP (27, 48, and 80 months, respectively). MRD negativity assessed at day 100 post autologous stem cell transplant is associated with improved PFS and OS in MM.

A 1-year survival benefit was demonstrated for each 1-log depletion in tumor burden by MFC [5]. Patients with adverse cytogenetics had slightly insignificant lower MRD than favorable cytogenetics [1].

Limitation of MRD Detection

MRD detection in the bone marrow has limited value when patients relapse outside the bone marrow with a genetically disparate clone. PB CTC single cell analysis would be useful in this situation. Whether MRD monitoring in the peripheral blood will be able to capture clonal diversity via single cell sequencing is highly needed to be investigated [2].

What Are the Next Steps for the MRD Field in Multiple Myeloma

Important tasks for the (near) coming future are as follows

1.Standardization efforts are needed. Prospectively validated flow-MRD approaches are still missing. The proposed Consensus recommendations and guidelines still rely on subjective 'expert-shared' knowledge and experience, which do not completely solve the lack of technical standardization [8].

2. Development of new, better and more sensitive MRD assays—for bone marrow aspirates and non-bone marrow aspirate-based assays (e.g., blood-based and imaging-based MRD assays) is required [12]. Assessment of MRD in PB is the ultimate goal since it allows serial sampling and avoid the invasive BM procedure [7] and its potential sampling error (i.e., false-negative results) [12].The sensitivity of MRD detection in PB and the optimal method to be used [12] are unknown. Clinical studies are recommended to explore PB use for the detection of MRD [7].Exploratory analysis of MRD in BM at more than one time point is also recommended [7].

3. Head-to-head comparisons of different types of assays will be critical [12] like comparing the results of PB with that obtained in BM [7]. Standardization of response definitions by PET as well as comparison with other sensitive BM-based MRD methods is needed to implement this imaging technique across different clinical studies. PET data interpretation can be a challenge considering heterogeneity of visual criteria and poor interobserver reproducibility [9].

4. Determine the prognostic importance of MRD status in relation to other known prognostic factors [5]

5. Further research on the role of MRD as a surrogate for prolonged OS among high-risk patients is warranted, since it could improve the typical poor prognosis of this patient population [4].

6. Assessment of MRD kinetics over the disease course (e.g., consolidation or maintenance therapy) instead of a single time-point when CR is first documented. This may determine the impact of different treatment approaches on MRD status and provide a better evaluation of disease control [7].

7. To define the exact details of MRD in the regulatory setting, (i.e., to define the amount of improvement in MRD negativity between the experimental arm and the control arm at a given time-point for a drug in the randomized studies to obtain regulatory accelerated approval [12]. It is just a matter of time until MRD negativity, becoming a regulatory end point for drug approval in newly diagnosed multiple myeloma [13].

8. Design novel clinical studies to formally assess the effect of MRD negativity in clinical decision making [12].For example, use of achieved MRD negativity as a tool to decide less intense therapy, and consider early relapse therapy when MRD negativity is converted to MRD positivity [12].

Emerging Techniques for Detection of Clonal Populations in Myeloma

Time of Flight Mass Cytometry

It combines flow cytometry with time-of-flight mass spectrometry. This technology uses antibodies labeled with stable heavy metal isotopes which allow assessment of large panels of markers.

Mass Spectrometry (miRAMM): This technique uses mass spectrometry to improve the analytical range of M-protein detection from peripheral blood in MM patients. Benefits of this method include use of peripheral blood, cost effectiveness, and rapid processing time. This technique can achieve sensitivities up to 10^{-7}

Conclusion

MRD could be used as a more potent surrogate biomarker for survival than standard CR. Standardization of the timing of MRD assessment, particularly as an early readout of efficacy among clinical trials will be important.

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