Minimal Residual Disease: Predicting and Preventing Relapse in Myeloma

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In the evolving landscape of haematologic cancers, the concept of minimal residual disease, also known as measurable residual disease (MRD), has rapidly shifted from a theoretical indicator to a powerful, practice-changing tool. At the forefront of this shift is multiple myeloma (MM), where MRD has emerged as a highly sensitive measure of treatment response and a compelling surrogate marker for long-term outcomes.

MINIMAL RESIDUAL DISEASE AS A SURROGATE MARKER FOR MYELOMA OUTCOMES

Opening this insightful session, Maria-Victoria Mateos, University of Salamanca, Spain, discussed the role of MRD in MM. She initially touched on The International Myeloma Working Group response criteria, a standardised set of parameters used to assess a patient's treatment response for MM. The treatment responses range from stringent complete response to progressive disease. These are based on laboratory values, imaging, and bone marrow analysis.

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Drawing on her own research published in 2017, Mateos and colleagues evaluated the impact of depth of response in newly diagnosed MM.[1] Data from 609 patients were analysed, with a median follow-up of 71 months. Results showed that MRD-negativity was a stronger prognosis predictor of PFS and OS than complete remission alone. It was therefore recommended that MRD negativity should be a determinant of treatment efficacy and a key goal when treating eligible patients with MM.

With the rise of new treatments and higher complete response rates in MM, the International Myeloma Working Group (IMWG) updated response criteria in 2016 to include MRD negativity.[2] More sensitive techniques, such as flow cytometry, gene sequencing, and imaging were used to define MRD negativity. The IMWG incorporated both next generation flow and next generation sequencing, with studies demonstrating good concordance between the two techniques.[3]

Mateos spotlighted two key initiatives: International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i^{2}TEAMM) and Evaluating Minimal Residual Disease as an Intermediate Clinical Endpoint for Multiple Myeloma (EVIDENCE) Meta-Analysis. i^{2}TEAMM, a collaborative research group advocating for MRD as an early endpoint in clinical trials for MM, published data in 2025. In this analysis, data from over 4,700 patients across 11 clinical trials were analysed to assess MRD-negative complete response (MRD-CR) as an intermediate end point for PFS and OS in three distinct populations: newly diagnosed (ND) transplant-eligible (NDTE), ND transplant-ineligible (NDTinE), and patients with relapsed/refractory MM.[4]

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Similarly, EVIDENCE Meta-Analysis evaluated whether MRD negativity could predict long-term outcomes in MM. Analysing data from 12 randomised trials, eight of which were studies on newly diagnosed multiple myeloma and four of which were studies on relapsed/refractory MM, the findings revealed strong associations between MRD-negativity and improved PFS, supporting its use as an early clinical endpoint to accelerate drug approvals.[5]

Importantly, Mateos offered a balanced perspective by highlighting some current limitations of using MRD as a surrogate endpoint in MM clinical trials. Currently, its acceptance is limited to the USA, where in April 2024 the FDA's Oncologic Drug Advisory Committee (ODAC) endorsed MRD as an acceptable endpoint for accelerated approval. Mateos noted ongoing efforts in Europe to adopt similar regulatory standards. She also emphasised that imaging methods to assess MRD, both inside and outside the bone marrow, are underutilised and should be integrated in future studies. Finally, the concept of sustained MRD negativity remains unexplored. The PERSEUS Phase III trial, evaluating daratumumab plus bortezomib, lenalidomide, and dexamethasone (VRd) in newly diagnosed MM, showed higher rates of sustained MRD negativity (at sensitivities of 10^{-5} and 10^{-6}) compared to the control group.[6,7]

Finally, Mateos cautioned that focusing solely on MRD negativity can overlook important factors such as toxicities and quality of life. She cited the BELLINI study, which tested venetoclax, an oral BCL-2 inhibitor, in combination with bortezomib and dexamethasone in patients with relapsed or refractory MM.[8] Despite improved PFS in the venetoclax group, it also reported a higher mortality rate. Finally, she highlighted that the minimal difference in MRD negative rates between two treatments or therapeutic strategies needed to ensure a (later) significant difference in PFS remains unclear.

MEASURABLE RESIDUAL DISEASE IN MYELOFIBROSIS

Nico Gagelmann, University Medical Center Hamburg-Eppendorf, Germany, subsequently delved into the role of MRD in myelofibrosis (MF), a blood cancer characterised by the abnormal accumulation of scar tissue, or fibrosis in bone marrow.

Gagelmann explored the genetic drivers and molecular pathophysiology of blood cancers, specifically myeloproliferative neoplasms.[9] The most common mutations

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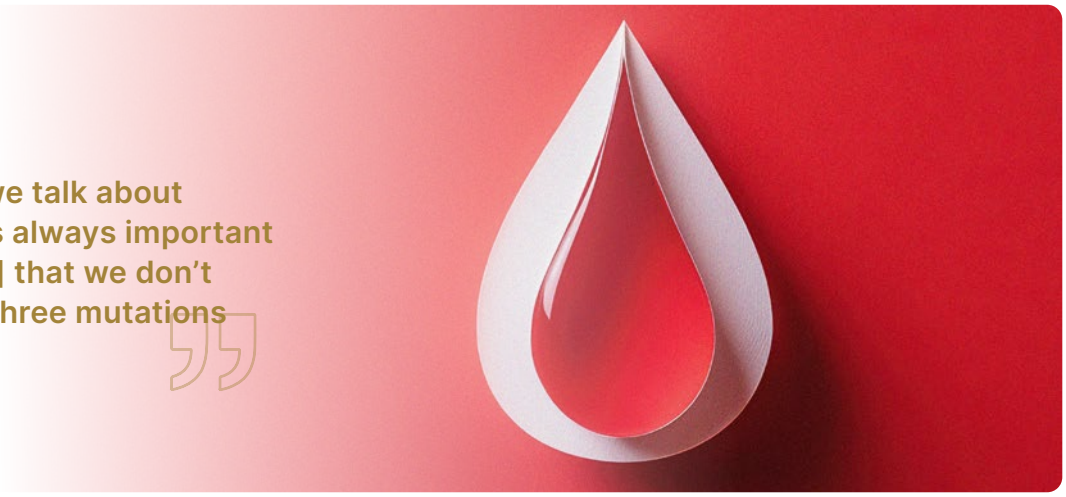

occur in three driver genes; *JAK2*, calreticulin (*CALR*) and myeloproliferative leukemia virus (*MPL*). "However, when we talk about myelofibrosis, it's always important [to acknowledge] that we don't have only these three mutations," stressed Gagelmann. He pointed to a range of cytogenetic abnormalities and high molecular risk mutations (*IDH1/2, EZH2, DNMT3A, U2AF1, SR5F2, TET2 and ASXL1*), which have been found to have an impact on both overall survival and progression to leukaemia.[9,10]

Quantitative PCR can be used to detect the presence of the three driver mutations (*JAK2*, *CALR,* or *MPL*) in patients with high sensitivity.[11] Drawing on his own research, Gagelmann and colleagues examined mutation clearance post-transplantation in 324 patients with myelofibrosis (73% *JAK2*, 23% *CALR*, 4% *MPL*). Mutations were assessed before transplantation, and at 30-, 100- and 180-days post transplantation. Interestingly, by Day 30, mutation clearance was found in 42% of *JAK2*, 73% of *CALR*, and 54% of *MPL* cases. Moreover, the cumulative incidence of relapse at 1 year was just 6% among patients with mutation clearance at Day 30, compared to 21% in those without.

So, how should we approach relapse? In a 2023 study investigating the effect of donor lymphocyte infusion (DLI) in 37 patients with molecular or haematological relapse after hematopoietic cell transplantation, results showed that molecular monitoring together with DLI allowed for early detection of relapse and was recommended as standard of care for relapsed myelofibrosis after HCT.[11]

TIMING DILEMMAS IN ACUTE MYELOID LEUKAEMIA: MINIMAL RESIDUAL DISEASE MONITORING AND STEM CELL TRANSPLANTATION

To close, Francesco Buccisano, University of Rome Tor Vergata, Italy, spoke on the incorporation of MRD in the different stages of allogeneic stem cell transplantation (allo-SCT). As highlighted by Buccisano, the methods for detection of MRD in acute myeloid leukaemia (AML) have also improved over the last decade.[13] He highlighted how multi-parameter flow cytometry (MFC) can be applied to almost 90% of patients with AML with a fair sensitivity of 10^{-3}–10^{-4}. Real-time quantitative PCR is another established technique, with a higher sensitivity (10^{-4}–10^{-5}) but lower applicability (40–50% of patients with AML) compared to MFC.

Buccisano outlined three key principles for selecting patients with AML for allo-SCT. First, identify those likely to respond well to chemotherapy alone to avoid overtreatment. Second, recognise patients with poor chemotherapy outcomes who would benefit from allo-SCT. Finally, ensure transplantation is feasible by assessing whether it can be performed, and the risk of morbidity and mortality is acceptable.

Data from over **4,700 patients** across **11 clinical trials** were analysed to assess MRD-negative complete response (MRD-CR) as an intermediate end point for PFS and OS

Notably, he discussed the role of MRD and novel agents at different stages of the treatment pathway in AML. Buccisano discussed the strategic use of MRD assessment throughout the allogeneic stem cell transplant process; pre-transplant, peri-transplant, and during post-transplant follow-up. While acknowledging the absence of randomised controlled trials due to ethical concerns around withholding transplants from patient who are MRD-positive, he presented data from hybrid study designs and large cohort analyses.

MRD positivity before transplant is consistently shown to be a strong predictor of relapse and poorer survival. Trials such as FIGARO attempted to intensify conditioning regimens in MRD-positive patients, but failed to improve outcomes, reinforcing the importance of MRD as a prognostic marker.[14] Importantly, the immunological environment, including T cell chimerism, can influence the impact of MRD, suggesting that graft-versus-leukaemia effects play a significant role in disease control.[13]

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> **MRD has shown to be a practical, prognostic, and increasingly regulatory tool in multiple myeloma and beyond**

Guidelines increasingly support the use of intensive conditioning for MRD-positive patients and advocate for tailored maintenance strategies post-transplant. Data from a study published in 2025 also demonstrated that MRD positivity before transplant predicts relapse, even in patients who appear MRD-negative at day 100 post-transplant.[15] This highlights the potential benefit of early intervention and maintenance therapy, such as sorafenib, which has shown efficacy in both MRD-negative and MRD-positive settings.

Although the MORPHO trial did not meet its primary endpoint, it supported the use of MRD as both a prognostic and predictive biomarker, particularly for guiding targeted therapies like gilteritinib.[16] Concluding his talk, Buccisano emphasised that MRD assessment, combined with genetic profiling, should guide risk stratification and treatment planning.

CONCLUSION

MRD has shown to be a practical, prognostic, and increasingly regulatory tool in multiple myeloma and beyond. As shown across studies and trials, achieving MRD negativity strongly correlates with better outcomes, offering a clearer path to tailored treatment and earlier decision-making. While challenges remain, its growing role signals a shift toward more precise, response-driven care in haematologic cancers.

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