Commentary

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Minimal residual disease in multiple myeloma: are we there yet?

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Multiple myeloma (MM) is one of the common hematological malignancies and, according to SEER data, 32,000 newly diagnosed cases are reported per year. It accounts for 1.8% of all cancers and around 17% of all hematological malignancies in the USA [1]. The presentation of MM is variable, with patients usually presenting with back pain, anemia and/or renal failure, while a small percentage of patients present with explosive clinical course, which can be life threatening. Despite several new drugs being approved by the US FDA (MD, USA) in the past few years, MM remains incurable and the overall survival (OS) of newly diagnosed high-risk MM patients is poor. Some of the challenges in achieving long-term remission or potential cure in MM patients are intraclonal and interclonal heterogeneity and lack of reliable indicators of deep treatment response. Minimal residual disease (MRD) assay is one such tool for measuring deeper response to treatment which, if sustained, could pave the way for cure.

In an attempt to facilitate accurate comparison of novel treatment strategies, in 2006 the International Myeloma Working Group (IMWG) developed the first international consensus criteria for response evaluation in MM based on the guidelines published by the European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry (EBMT/IBMTR) in 1998 [2,3]. Complete response (CR) was defined as absence of monoclonal protein in the serum and/or urine and bone marrow showing less than 5% plasma cells. To refine the response assessment, the 2011 IMWG guidelines introduced four-color flow cytometry and allele specific oligonucleotide-PCR (ASO-PCR) to define immunophenotypic CR and molecular CR as new criteria [4]. This could be considered an early version of today's MRD. Attainment of CR using the conventional serological and morphological assessment has been shown to result in prolonged survival [5]. However, MM is still incurable and several patients experience disease relapse eventually. This highlights the fact that the current tools of assessment of tumor burden cannot measure the disease in its entirety and it is this small population of myeloma cells termed residual disease that could lead to relapse. This has led to efforts to create tools, both imaging and molecular, which are more efficient to evaluate deeper responses that eventually culminated in the concept of MRD. IMWG, in their updated consensus response criteria in 2016, has further clarified several aspects of MRD assessment, methods of MRD detection and expanded the response criteria by incorporating imaging-based MRD negativity to rule out the presence of extramedullary disease [6].

Methods to measure MRD can be broadly classified as molecular methods that measure medullary disease (disease in the bone marrow) and imaging techniques that measure extra medullary disease (disease outside the marrow). Multiparameter flow cytometry (MFC), ASO-PCR and next-generation sequencing (NGS) measure residual disease using bone marrow aspirate. Imaging modalities such as MRI and PET-computed tomography (PET/CT) are used to assess extra medullary disease.

MFC relies on the distinction of malignant plasma cells from normal plasma cells based on the expression of a range of phenotypic aberrancies, such as the expression of cytogenetic differentiation markers [7]. Initially four-color and six-color panels were used and currently eight-color and ten-color antibody panels are used. The first report of the prognostic value of MRD measurement in MM using MFC was made by Rawstron and San Miguel separately in 2002 [8,9]. MRD status based on MFC with a sensitivity of 10^{-4}–10^{-5} has been shown to have a significant impact

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on the outcomes of myeloma, both in the newly diagnosed and relapsed settings [10]. MFC is widely available, has higher applicability and does not require patient-specific diagnostic phenotypic profiles [11]. However, the lack of a well-standardized method using a single validated antibody panel, at least in the USA, is a major disadvantage of MFC that makes comparison between institutions difficult. A sufficient number of cells need to be evaluated to avoid the possibility of a false-negative MRD.

Next-generation flow, based on Euroflow, which utilizes bulk lysis procedure to increase sample cellularity and novel software tools for plasma cell gating has emerged as a more sensitive and highly standardized approach for MRD detection. In a recent study, next-generation flow-MRD was shown to have a higher sensitivity versus conventional eight-color flow-MRD (MRD-positive rate of 47 vs 34%; p = 0.003) [12]. ASO-PCR relies on the identification of persistent tumor cells through the amplification of the immunoglobulin heavy chain gene rearrangement. It is well-standardized, making it reproducible, and has higher sensitivity (10^{-5}–10^{-6}) compared with MFC but is technically challenging, expensive and not widely available making it a less popular method in routine practice. Nevertheless, the clinical utility of this method in prognosing the outcomes of myeloma was shown by Puig *et al.* [13].

NGS relies on the amplification and sequencing of immunoglobulin sequences using consensus primers and using software algorithms. Such disease-related sequences are quantified yielding a sensitivity of 10^{-6}, making it the most sensitive method currently available for detection of MRD. Patients with myeloma achieving MRD negativity by NGS were shown to have improved progression-free survival (PFS) and OS in both transplant and non transplant settings [14]. More importantly, Martinez and colleagues showed an improvement in time to progression with log reduction in MRD level. However, NGS is expensive, labor-intensive and is not widely available for clinical practice yet.

Imaging modalities such as MRI and 18-Flourodeoxyglucose PET (FDG-PET) have emerged as significant tools to measure MRD in the last few years. These provide information regarding disease involvement of the bones, pattern of bone marrow involvement, as well as disease outside the marrow (extra medullary disease). This becomes relevant in patients with negative MRD based on molecular assessment of the bone marrow with patchy involvement or presence of extra medullary disease.

MRI is the most sensitive imaging technique for detection of myelomatous lesions in the spine. However, the disease response by imaging lags behind serological response, and tumor necrosis and inflammation following treatment could result in focal lesions being hyperintense for a while, leading to patients being MRD negative by molecular testing but positive by imaging.

FDG-PET/CT has the added advantage of combining functional assessment of disease as measured by FDG uptake and the morphological assessment of skeletal lesions with the CT. PET/CT has been shown to have similar sensitivity as whole-body MRI with increased specificity [15]. Several studies have shown the utility of PET/CT in MRD monitoring in both the pre and post-transplant settings. In a study conducted by Zamagni *et al.* evaluating the role of PET/CT at diagnosis, post-induction and post-tandem transplantation in newly diagnosed multiple myeloma (NDMM) patients, presence of at least three focal lesions, a standardized uptake value of >4.2 and extramedullary disease at baseline portended a poor PFS and presence of extramedullary disease was also associated with a poor OS [16]. Persistent uptake on FDG-PET has been shown to predict an early relapse in the post-transplant setting. Due to the significant role of FDG-PET in monitoring residual disease in myeloma, IMWG guidelines have now included an 'Imaging plus MRD-negative' criterion to include a CR by PET-CT along with a negative next generation flow or sequencing technique [6]. There are still several limitations to this method that need to be overcome. There is a lot of variability in the methods used to measure standardized uptake value, response criteria and interpretation of response. In addition, unlike for solid tumors (PERCIST) and lymphomas (Deauville), standard criteria to evaluate response of the focal lesions in MM are lacking. Due to the metabolic nature of the tracer, conditions like hyperglycemia due to diabetes mellitus or from the high-dose steroids as part of MM therapy could result in false negatives. For the same reason, false positives are often seen with infection, inflammation and post-surgical states. Recent data show that FDG-PET might not be the best imaging method for response assessment in patients receiving immune targeted therapies [17].

Several studies have been done showing the impact of achieving MRD negativity on the outcomes of patients with MM. Landgren *et al.* in their first meta-analysis in 2016 showed a 50% improvement in PFS for patients with NDMM achieving MRD negativity [18]. Later, in 2017, Munshi and colleagues conducted a larger meta-analysis involving patients with NDMM that showed that attaining MRD-negative status after treatment was associated with long-term survival. They also noted that the best OS was seen in patients with favorable cytogenetics who

achieve MRD negativity compared with patients who have high-risk cytogenetics or remain MRD positive, while patients having both these have the worst outcomes [19]. Updated results from the large Phase III randomized IFM study in 2017 confirmed that PFS benefit from MRD negativity was independent of the therapy used and showed that autologous stem cell transplantation did not improve PFS or OS in patients who already achieved MRD negativity by NGS after induction therapy with VRd (velcade, revlimid and dexamethasone) [20]. The effect of MRD negativity on the outcomes is agnostic of the treatment regimen used or the method of determination. A Phase III study of transplant-ineligible patients with NDMM by Mateos *et al.*, where patients received induction therapy with VMP (velcade, melphalan and prednisone) followed by randomization to daratumumab or control group, showed that achieving MRD negativity by NGS (sensitivity of 10^{-5}) led to an improved 18-month PFS of 72% in the treatment group and 50% in the control group [21]. MRD status has been included in several randomized clinical trials in the relapsed/refractory setting recently. In the CASTOR study, patients treated with bortezomib, dexamethasone and daratumumab achieved higher MRD negativity (NGS with a sensitivity of 10^{-5}) compared with bortezomib and dexamethasone (14 vs 2%) that led to a PFS benefit (16.7 vs 7.1 months) at a median follow-up of 40 months [22]. In the POLLUX study, randomizing RRMM patients to lenalidomide and dexamethasone ± daratumumab, patients on the daratumumab arm had higher MRD negativity compared with the control group (10^{-5}, 30.4 vs 5.3%) and a higher 42-month PFS (76.7 vs 42.8%) [23]. In both these studies, PFS benefit was agnostic of the treatment received as long as the patients were negative for MRD, showing the relevance of MRD testing even in RRMM population. It is to be noted that maintaining MRD negativity, not just achieving it, is more important and a step toward functional cure for MM [24].

There is extensive data available now on the impact of MRD negativity on long-term outcomes in both newly diagnosed and relapsed myeloma. However, it is not ready for use in clinical practice yet. There are several unanswered questions before we can change standard of care therapy based on MRD: does treatment modification based on change in the status or level of MRD alter outcomes and if so, what is a clinically significant change?; what are the optimal MRD goals at different time points during the treatment?; how can we overcome the possibility of false-negative MRD results due to the spatial heterogeneity with patchy involvement of bone marrow in MM?; and what are the optimal frequency and sample source (bone marrow vs peripheral blood) of MRD testing?

Clinical trials are underway to answer these and several other questions. For example, Costa *et al.* are investigating the strategy of response-adapted treatment based on MRD status in NDMM following induction therapy, autologous stem cell transplantation and during maintenance therapy in the MASTER trial [25]. There is ongoing research to develop MRD testing using peripheral blood by looking for circulating tumor cells or cell-free DNA. Such well-designed trials could provide data to guide us in the management of MM better. For example, MRD negativity could play a potential role in determining patients with NDMM who can defer stem cell transplantation, patients in whom maintenance therapy can be discontinued or patients with RRMM who can be transitioned to less intense therapy after achieving sustained MRD negative remission. This concept of personalized treatment based on dynamic risk and response assessment with MRD testing could avoid prolonged treatment, often with multiple drugs, thereby reducing the toxicity and financial burden associated with it.

With the approval of several new drugs with different mechanisms of action and the incorporation of MRD as an end-point in clinical trials, the management landscape of MM is changing rapidly. Given the significant impact of MRD negativity on the outcomes, it could be a new regulatory surrogate end-point for survival in clinical trials and a main driver of research and clinical practice in MM in the future.

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