REVIEW ARTICLE

Role of minimal residual disease assessment in multiple myeloma

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Abstract

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells. MM is a heterogeneous disease, featured by various molecular subtypes with different outcomes. With the advent of very efficient therapies including monoclonal antibodies, bispecific T-cell engagers and chimeric antigen receptor T cells (CAR T cells), most MM patients now have a prolonged survival. However, the disease remains incurable, and a subgroup of high-risk patients continue to have early relapse and short survival. Novel and highly sensitive methods have been developed allowing the detection of minimal residual disease (MRD) during or after treatment. Achievement of MRD negativity is a strong and independent prognostic factor in both prospective randomized clinical trials and in the real-world setting. While MRD assessment is now a validated endpoint in clinical trials, its incorporation in clinical practice is not yet established and its potential impact on guiding therapy remains under in-depth evaluation. Here we discuss the different methods available for MRD assessment and the role of MRD evaluation in MM management.

Introduction

Multiple myeloma (MM) is a heterogeneous disease characterized by more than 10 distinct molecular subtypes associated with variable outcomes.[1] The therapeutic landscape of MM has dramatically changed over the last five years. The incorporation of monoclonal antibodies, first in the relapse setting, and more recently in front-line treatment in a triplet or quadruplet regimen, the approval of chimeric antigen cell (CAR) T-cell therapy, and the recent approval of bi-specific monoclonal antibodies or T-cell engagers have revolutionized MM treatment and prognosis.[2-4] With more than 14 drugs approved by the US Food and Drug Administration (FDA), there are now various treatment options and most MM patients now have prolonged survival.[2] However, MM remains incurable and therefore the ability to identify high-risk patients, and to appropriately sequence therapy based on disease characteristics and response to treatment is critical. Along with plasma cell molecular and cytogenetic characteristics, response to treatment is another major prognostic factor, and its assessment is an essential part of patient care. The definition of hematologic response has evolved in the past 20 years with the incorporation of novel highly sensitive methods to allow comparison of treatment strategies in clinical trials. International consensus criteria defining hematologic response in MM were first established in 1998 and revised in 2016, especially to incorporate the free light chain (FLC) dosage. The original definition of a complete response (CR) only required bone marrow (BM) to have <5% plasma cells, irrespective of their clonal nature, while the 2016 criteria defined CR as negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in BM aspirates. Stringent CR was defined as CR plus normal FLC ratio and absence of clonal cells in BM biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). Overall, achievement of CR is associated with a significantly prolonged period of progression-free survival (PFS) and overall survival (OS).[5] However, not all patients achieving CR have a good prognosis as some patients achieving CR unfortunately have early relapse or progression. The concept of minimal residual disease (MRD) which refers to the ability to detect a very small

number of malignant plasma cells during or after treatment was adopted in the International Myeloma Working Group (IMWG) consensus criteria in 2015 to provide more accurate hematologic response assessment. Since then, MRD evaluation has been shown to significantly improve hematologic response evaluation and to improve prognostic stratification after therapy in newly diagnosed transplant eligible and transplant non-eligible patients and in relapsed disease. The prognostic role of MRD is now well documented and has been demonstrated in several retrospective and prospective studies, and MRD negativity is now an established criteria in MM clinical trials. However, the impact of MRD assessment on treatment decisions remains to be determined and is currently under in-depth investigation in several randomized clinical trials.[6-16] In addition to BM-based MRD evaluation, novel techniques utilizing whole body imaging (WBI) and blood-based evaluation have been developed and will likely improve MRD evaluation in MM patients. Here, we describe the different methods available to assess MRD, and discuss the clinical applications and challenges of using MRD in clinical practice.

Bone marrow-based minimal residual disease assessment

Next-generation flow cytometry

First MRD evaluation was performed by multiparametric flow cytometry (MFC), a technique available worldwide able to identify monotypic plasma cells in the BM even if present at a low level.[17,18] Conventional MFC MRD approaches usually use 4-10 cell markers (colors) but are limited by relatively low sensitivity, absence of standardization, and lack of reproducibility. Therefore, next-generation flow cytometry (NGF), a more sensitive method, was developed and standardized by EuroFlow to overcome most of the conventional MFC limitations.[19-21] NGF is based on a more efficient sample preparation protocol for acquisition of up to 10 million BM cells and uses 8-12 colors characterizing most cellular subtypes and normal plasma cells (CD138 and CD38) and aberrant plasma cell markers (CD20, CD56, CD19, CD45, CD27, CD28, CD33, and CD117). Additionally, intra-cytoplasmic markers for κ or λ immunoglobulin light chains are used to confirm monotypic or clonal cells. Importantly, NGF high sensibility allows detecting one abnormal plasma cell out of 10^-6 cells and does not require a sample at the time of diagnosis.[21] It is also adapted to patients receiving anti-CD38 therapy, despite the potential interference with plasma cell detection.[21] Standardized data analysis methods allow for an increased sensitivity and reliability. The clinical impact of high-sensitivity MRD detection by NGF has been validated in randomized clinical trials and in real-world patients with MM.[19,22] In the GEM/PETHEMA trials, only 7% of patients achieving MRD-negativity (MRD <2 10^-6 cells) were reported to have disease progression with half of those patients progressing with extra-medullary disease (EMD). Achievement of MRD negativity was associated with an 82% and 88% reduction in the risk of progression and death (Hazard Ratios [HR] of 0.18 and 0.12; P<0.001), respectively. Importantly, MRD negativity overcame the poor prognostic value of high-risk cytogenetics at diagnosis.[19] The EuroFlow NGF approach has now been validated by the IMWG as the reference flow cytometry method to evaluate MRD negativity after therapy.[5] The EuroFlow process, which uses 2-tube 8-color methodology, is widely used in Europe, Asia and the US. However, several groups, especially in the US, have developed other methods, using single-tube, 10- or 12-color methods that are similarly efficient, more cost-effective, and conform to the IMWG and National Comprehensive Cancer Network guidelines.[23]

Next-generation sequencing

High-throughput DNA sequencing methods developed to study B- or T-cell receptor repertoire have been applied to MM. These methods can identify one malignant cell in 1 million analyzed cells (10^-6). The Adaptive Biotechnologies (clonoSEQ) NGS assay is currently the only assay cleared by the FDA for MRD evaluation in BM from patients with MM. NGS can detect clonotypes that are defined by sharing identical immunoglobulin gene sequence reads with a frequency ≥5%. This strategy requires an initial BM sample to identify the predominant clone, and allows the myeloma clone to be detected in 90-92% of myeloma patients.[16] The prognosis value of achieving NGS-based MRD negativity has been demonstrated in several randomized trials. In the Intergroupe Francophone du Myélome 2009 trial, MRD negativity was a strong prognostic factor for both PFS (adjusted HR: 0.22; 95% Confidence Interval [CI]: 0.15-0.34; P<0.001) and OS (adjusted HR: 0.24; 95% CI: 0.11-0.54; P=0.001). Patients who were MRD negative had a higher probability of prolonged PFS than patients with MRD-positive disease and a cytogenetic risk profile, regardless of the treatment arm or International Staging System disease stage at diagnosis. The level of MRD correlated with outcome, and the deeper the level of MRD (<10^-6), the better the prognosis.[16] A pooled analysis searching for associations between patients achieving CR or better (≥CR) with MRD-negative status and PFS from 4 randomized clinical trials, confirmed that relapsed/refractory MM (RRMM) and transplant ineligible newly diagnosed MM (TIE NDMM) patients achieving ≥CR with MRD negativity had a significant PFS benefit (NDMM and RRMM HR: 0.20; P<0.0001; TIE NDMM and RRMM ≤2 PL HR 0.20, P<0.0001).[14] Remarkably, achievement of MRD negativity is, independently of the study arm, associated with best and similar outcome in newly diagnosed MM patients who are transplant eligible and transplant ineligible, as well as in relapse refractory disease.[14,15] These data strongly support the concept that achieving MRD negativity may be more important than how it was actually achieved.

Bone marrow MRD assessment requires repeated invasive procedures, and is limited by the known patchy nature of MM and the possibility of EMD that are inherent to the disease. Therefore, alternative approaches including blood or imaging-based MRD evaluation assessment have been developed.[24]

Blood-based minimal residual disease assessment

Circulating plasma cells

The presence of circulating plasma cells (CPC) in peripheral blood (PB) can be detected in most MM patients and is associated with poor prognosis. Different methods have been used to assess the presence of CPC. The standard EuroFlow NGF is reliable and requires a small volume of blood. Other methods are available that use a plasma cell enrichment method, which requires a larger blood sample, and is more sensitive but also more complex. NGF has been used to identify and track CPC in MM patients with interesting results. However, while CPC detection appears to be a powerful prognostic factor, CPC is unlikely to be a good MRD marker. Indeed, a comparison between NGF in BM and PB after therapy in a real-world case series of 137 patients showed that 40% of patients achieving blood-based MRD negativity had BM MRD-positive disease, strongly suggesting that blood NGF-based MRD evaluation is a less sensitive MRD marker than BM MRD.[22,25,26]

Circulating cell-free DNA for minimal residual disease assessment

Circulating cell-free DNA (cfDNA)-based methods, often referred to as 'liquid biopsy', allow tracking genomic aberrations such as tumor mutations, copy number aberration or translocation present in circulating cfDNA isolated from blood plasma.[27-29] Multiple studies showed a high concordance of somatic mutations and copy-number alterations between BM and cfDNA of patients with MM.[30-33] However, the low level of circulating tumor DNA is a significant challenge and most current methods are not sensitive enough. Ultradeep targeted sequencing has significantly improved the detection of cfDNA, but its sensitivity relates to the number of tumor mutations available to track and has so far only been evaluated in few clinical studies. In a study which compared blood and BM evaluation with NGS and cfDNA in 42 patients, there was only 49% consistency and poor correlation between the two methods. Similar to CPC detection, BM MRD was more often positive and suggested lack of sensitivity of the cfDNA approach.[34] Novel and more sensitive methods are needed before cfDNA can be utilized as a standard approach.

Single-cell RNA sequencing

Single-cell RNA sequencing (scRNA-seq) is another powerful technology widely used in research. It allows transcriptomic analysis at a single cell level and can detect rare malignant cells.[35] Ongoing research is investigating whether this approach could even allow the selection of therapy based on transcriptomic features and clonal heterogeneity.[36,37] However, its availability, its relative complex workflow, reproducibility and cost are significant challenges that need to be addressed before it can be considered for use in clinical practice.[38] This approach is also limited by the fact that it can currently only evaluate a certain number of cells, far fewer than with flow- or NGS MRD-based assessment methods. Therefore, the lack of detection of malignant cells would not necessarily correspond to negative MRD, and scRNAseq appears more as a potential complimentary method that may help tailor therapy to target MRD positive cells rather than to determine MRD status.

Mass spectrometry methods

Instead of tracking the malignant residual plasma cell, mass spectrometry (MS) methods have been applied to detect the monoclonal immunoglobulin produced by the malignant plasma cells. This very sensitive method can detect the presence of a monoclonal immunoglobulin at a much lower concentration than standard serum immunofixation. MS can also distinguish therapeutic monoclonal antibodies from myeloma monoclonal immunoglobulin, and can identify post-translational modifications relevant for patients with monoclonal gammopathy of clinical significance, including light chain (AL) amyloidosis.[39-41] Several MS methods have been developed. Matrix-assisted laser desorption/ionization MS (MALDI-TOF MS) and the MASS-FIX assay have been shown to be particularly efficient, and both more sensitive and more specific than serum protein electrophoresis and immunofixation.[40,42,43] Another MS approach was initially developed by the Binding Site company in collaboration with the Mayo Clinic. The Mayo Clinic went on to develop their own approach using a commercial assay, while the Binding Site assay, which has more selective probes, was sold to ThermoFisher and is used in individual labs. Methods using liquid chromatography-tandem mass spectrometry (LC-MS/MS) are currently under clinical investigation and are not yet FDA-approved. Other MS methods focusing on quantifying unique clonotypic peptides (MS-MRD) derived from the variable region of the monoclonal immunoglobulin by enzymatic digestion followed by LC-MS/MS have been developed and provide great sensitivity. MS-MRD demonstrated a 1,000-fold higher sensitivity compared to serum protein electrophoresis (SPEP) and can be used to monitor patients with MRD.[40,44-46] While some preliminary reports suggest that MS may be a strong predictor of PFS,[47] additional studies are needed to incorporate these assays into clinical practice. In particular, the persistence of the monoclonal immunoglobulin in the serum in the context

of BM MRD negativity detected by serum immunofixation or MS has been reported in different studies and may be related to the immunoglobulin half-life rather than to an MRD-positive disease. Therefore, incorporation of MS needs to be clarified.

Whole-body imaging and minimal residual disease assessment

While imaging studies do not allow the detection of active disease at the single cell resolution, relatively novel WBI techniques including positron emission tomography with computed tomography (PET/CT) and magnetic resonance imaging (MRI) allow a better characterization of bone lesions and EMD. PET/CT and whole-body MRI have been evaluated to assess residual disease after therapy.[48-51] Both methods are very sensitive and have been shown to complement BM-based MRD assessment considering the patchy nature of MM and its spatial heterogeneity. Patients presenting with EM lesions or with para-medullary plasmacytomas are at higher risk of developing EMD even in the context of BM MRD-negativity.[52] ^{18}Fluorodeoxyglucose (^{18}F-FDG)-PET is a very sensitive method to identify active disease, and several studies showed that PET-positive lesions after completion of therapy is associated with poorer outcome, while FDG-PET/CT negativity after autologous stem cell transplantation (ASCT) in patients achieving CR predicts a lower risk of progression or death.[53-56] Patients obtaining PET/CT normalization upon therapy have comparable prognosis to patients without baseline increased metabolism, suggesting the value of treating until suppression of glucose metabolism.[56] In the FORTE trial, a high concordance between PET/CT and NGS (84%) and between PET/CT and MFC (93%) at 10^−5 in the identification of BM residual disease was reported. By contrast, there was a discrepancy in the assessment of MRD in patients with focal lesions in approximately 33-37% of cases, suggesting that PET/CT alone might not be accurate enough.[57] Similarly, in the CASSIOPET study, a significant concordance between BM and PET/CT-based MRD assessment was reported in 109 patients, but the data suggested a higher sensitivity for the BM-based MRD method.[58] A standardized definition of PET/CT complete metabolic response has been proposed considering the uptake of the liver as threshold and is currently under confirmation in independent prospective series of patients.[48] A significant challenge related to ^{18}FDG PET/CT relates to the 10-15% of MM patients with no FDG-avid lesions due to lack of hexokinase enzyme, which is responsible for FDG trapping in the myeloma cells or to the absence of identified lesions.[59] New PET/CT tracers including CD38, radiolabeled antibodies and VLA-4 (*clinicaltrials.gov 03804424*) represent new, potentially more sensitive methods that are under investigation.[13,60,61] Along these lines, conjugating daratumumab with the positron emitting radioisotopes Copper-64 (64Cu) and Zirconium-89 (^{89}Zr) has allowed for the creation of immunoPET tracers. ^{89}Zr-Daratumumab has demonstrated an ability to detect MM cells or lesions when not detected by ^{18}FDG-PET/CT and other clinically standard imaging methods.[62,63] However, the lesser availability of these newer tracers, interpatient heterogeneity regarding specific targets, and lack of prospective data remain important challenges to be addressed.

Similar to PET/CT, presence of residual lesions after high-dose chemotherapy followed by autologous stem cell transplant (HDC-SCT) identified by whole body MRI (wbMRI) is associated with adverse prognostic significance.[64-66] MRI seems to be more sensitive in diagnostic methods to identify myeloma lesions than PET/CT. In a prospective study comparing PET/CT and wbMRI in 60 patients, wbMRI showed significantly higher detection of focal lesions at all anatomic sites (except ribs, scapulae, and clavicles) and of diffuse disease at all sites. However, MRI is not able to differentiate between vital and necrotic tissue within pre-existing osteolytic lesions[64] and therefore PET/CT positivity may be more accurate to assess MRD and to predict patient outcome.[67-69] A more sensitive MRI-based method called diffusion weighted imaging (DWI) is a promising alternative allowing more accurate detection of active lesions and is under investigation.[70,71] Whether MRD is assessed with PET/CT or wbMRI, the complementary role of imaging studies to BM-based MRD evaluations is significant and strategies to include both are being evaluated.

Based on the increasing amount of MRD data, and the availability, reproducibility and standardization of MRD methods, MRD assessment has become an important and validated criterion in clinical trials. MRD assessment is now used for patient selection, risk stratification or enrichment of clinical trial subgroups, and as an endpoint. MRD assessment will likely contribute to expedite drug development.[13] However, using MRD assessment to guide therapy and MRD incorporation in clinical practice is not yet validated. We here discuss some of the most significant challenges that have been or need to be addressed.

Which minimal residual disease method to use?

As discussed above, MRD assessment using BM-based methods remains the gold standard with increasing data regarding WBI. Availability, cost, prognostic power, and consistency are important factors to consider. Regarding BM-based MRD, NFC and NGS are the 2 methods of choice to evaluate BM MRD and both have been shown to constitute a strong prognostic marker in MM. Table 1 summarizes the main characteristics of these methods. Comparison between flow cytometry and NGS methods has been performed in randomized clinical trials. In the phase II multicenter randomized FORTE trial, 86% of correlation with MRD at a sensitivity of 10^−5 in patients ≥CR was reported.[72] In the phase III CASSIOPEIA trial, MFC and NGS were consistent in 83.5% with a sensitivity of 10^−5.[73] A direct comparison between NGF and NGS (not Clonoseq platform) was also reported in a study of 106 patients

Table 1. Available methods to assess bone marrow minimal residual disease in multiple myeloma.

BM-based MRD	NGF	NGS
BM evaluation	Yes	Yes
Standardization	Euroflow	Clonoseq
Evaluation required at diagnosis	Not required	Required
Fresh sample	Yes	No
Cost	+	++
Applicability	Universal	~90% of patients
Sensitivity	10^{-5}-10^{-6}	10^{-6}

BM: bone marrow; MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing.

Table 2. Available whole body imaging methods to complement bone marrow minimal residual disease assessment in multiple myeloma.

WBI methods	PET/CT	wbMRI
BM evaluation	No	No
Standardization	Yes	Yes
Evaluation required at diagnosis	Not required* Negative in ~10% of MM patients	Not required*
Cost	++	++
Applicability	++	+
Sensitivity	++	+++

BM: bone marrow; CT: computed tomography; MM: multiple myeloma; PET: positron emission tomography; WBI: whole body imaging; wbMRI: whole body magnetic resonance imaging. *Useful to have WBI at diagnosis to evaluate response. Important to confirm if PET/CT positive at diagnosis.

showing a high correlation (R^2 = 0.905).[74] As NGS and NGF are comparable, each method should be considered based on local availability. Complementary imaging methods to assess bone and EM MRD currently include wbMRI and PET/CT imaging, and provide additional information, while BM- and WB imaging-based methods have relatively good concordance and provide additional information, particularly regarding EMD and high-risk MM. WBI should, therefore, be used in combination with BM-based MRD in patients with high-risk or EM disease. Table 2 summarizes the characteristics of WB imaging methods. Some studies now support the benefit of combining both MRD methods in patient care.[71]

When should minimal residual disease assessment be performed?

Another important challenge regarding MRD utilization relates to its timeline. A first question is whether MRD evaluation should be done early during front-line treatment (for example, before SCT) or later on (after consolidation or during maintenance). Several trials have evaluated each of these time points, and because of the dynamic nature of MRD which implies transition from MRD positivity to negativity and vice-versa, it has become clear that several evaluations are, in fact, more informative. These observations led to define the concept of 'sustained' MRD negativity which appears to be the critical prognostic factor in MM.[75] Having defined this concept led to another important question, which is how much time should pass between the 2 time points. It seems that longer time points will likely be associated with better outcome, and studies are investigating if six months, one year or two years of MRD negativity are more relevant to potentially impact treatment decision. For example, in chronic myeloid leukemia (CML), strategies to stop therapy after two years of sustained MRD negativity have been developed.[76,77] However, CML and MM are very different diseases biologically, and large phase III clinical trials are needed and are, indeed, ongoing to address this question. In future clinical practice, we anticipate that MRD assessment will be useful to evaluate the efficacy of a particular treatment strategy, before or after consolidation therapy or during maintenance in newly diagnosed myeloma and relapse/refractory disease. It is important to mention that the advent of cellular therapies including bi-specific antibodies and CAR T-cell therapy have revolutionized patient outcome and are associated with dynamic and often dissociated patterns of MRD and serological residual disease. Therefore, the role of MRD evaluation in the context of these novel therapies remains to be fully validated.[78]

How far is minimal residual disease evaluation useful in high-risk myeloma patients?

High-risk MM is defined by the presence of del17p, t(4;14), t(14;16), low albumin, high β2 microglobulin and elevated lactate dehydrogenase (LDH).[79] MM patients experiencing

early relapse after front-line therapy have also the poorest outcome.[80] Important studies are ongoing to improve treatment strategies in this subgroup of patients. Different results regarding clinical impact of MRD status in high-risk patients have been reported.[81,82] While achievement of MRD negativity is associated with clinical improvement in HR MM, it does not overcome its poor prognosis and HR MM may still have early progression. In addition, data from the large phase III trial (Myeloma XI) showed that high-risk molecular features had an adverse effect on PFS and OS even for those patients achieving MRD-negative status.[83] BM MRD evaluation only is likely to be insufficient to fully assess MRD, in the context of patchy disease and EMD, as discussed above. Indeed, in a study comparing BM and imaging-based MRD assessment, 12% of patients who achieved BM MRD negativity by flow cytometry had positive PET/CT or whole-body diffusion-weighted MRI (WB-DWI-MRI) and had a shorter PFS in comparison to patients with both BM and imaging MRD negativity.[56] Further data are needed to better interpret and use MRD status, especially in high-risk patients and patients with EMD. Sustained MRD and combined BM and imaging-based MRD assessment are important parameters to consider. Both sustained MRD negativity and combined BM and imaging MRD studies (PET/CT or wbMRI) appear to be the most valuable approaches in HR MM patients. Results from randomized trials are expected to address this important question. Similarly, in the context of RR MM, while achievement of MRD negativity is associated with better outcome, most of the patients do experience relapse. This is well illustrated by the KarMMa trial that evaluated the efficacy and safety of Idecabtagene vicleucel (ide-cel) in patients with RR myeloma, for example, in which 26% of the patients achieved MRD negativity, including 79% of patients achieving CR. However, only 40% of patients achieving at least CR were in remission at 20 months of follow-up.[84] It seems that sustained MRD negativity combined with WBI will be more relevant in that context.

Should minimal residual disease assessment be made only in patients achieving complete hematologic response?

Another important point relates to which patients should be evaluated for MRD. In clinical trials, MRD investigations were performed either in MM patients achieving CR or stringent CR or at specific timepoints of a given therapeutic protocol (e.g., before SCT, before or during maintenance). It was showed that patients achieving CR with MRD positivity had significantly worse outcome than patients achieving both CR and MRD negativity. However, several studies have reported MRD negative rates in MM patients achieving very good partial response (VGPR), and indeed, up to 25% of patients achieving MRD negativity assessed by either flow cytometry or NGS have persistent positive immunofixation and are, therefore, classified as VGPR.[85] Importantly, retrospective and prospective studies showed that patients with positive IF and MRD negativity have similar outcome to patients with negative IF and MRD negativity. The discrepancy between positive IF and MRD negativity may be related to several reasons, including EM disease, BM sample not representative of full BM or long half-life of the monoclonal immunoglobulin.[85] This is further highlighted in studies utilizing MS (the sensitive assay to detect monoclonal immunoglobulin described above). In one study, the monoclonal immunoglobulin was still detectable by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometer (MALDI-TOF) in 69% of patients who achieved a conventionally defined CR and were BM-based NGF-MRD-negative after 100 days from ASCT.[86] Finally, discordant MRD and IF results are frequently observed after CAR T-cell therapy, with low rates of CR observed in patients achieving MRD negativity, particularly in the first six months after treatment, suggesting that MRD evaluation which reflects the clearance of myeloma cells in the BM could be an independent prognostic marker in that setting.[78] Therefore, assessing MRD in patients achieving at least VGPR or better is very relevant and informative.

Should minimal residual disease status impact therapeutic decision-making?

Minimal residual disease negativity is a very strong and now established prognostic marker. However, its impact on therapeutic decision-making remains to be determined. Several randomized clinical trials are currently ongoing to address this question (Table 3). The goals of these trials are to determine if treatment should be adapted based on MRD status: intensification of treatment in case of MRD positivity, stop maintenance therapy in case of sustained MRD negativity or treatment change in case of MRD status conversion from negativity to positivity. The MASTER trial pioneered this strategy and evaluated the role of BM-based MRD in treatment during consolidation. Patients received combined daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) as induction therapy and BM MRD was performed by NGS at different time points (end of induction, after HDC-SCT, and every 4 cycles of consolidation) to inform the use and duration of treatment with Dara-KRd. Treatment was stopped in patients who achieved 2 consecutive MRD-negative assessments. Among 123 included patients, 43% had none, 37% had one, and 20% had 2 high-risk cytogenetic abnormalities (HRCA), and 96% had BM MRD trackable by NGS. With a median follow-up of 25.1 months, 80% of patients reached MRD negativity (78%, 82%, and 79% for patients with 0, 1, and 2+ HRCA, respectively), including 66% who reached MRD $<10^{-6}$, and 71% who reached 2 consecutive MRD negative assessments during therapy, entering treatment-free surveillance. Two-year PFS was 87% (91%, 97%, and 58% for patients with 0, 1, and 2 HRCA, respectively).

Table 3. Ongoing prospective clinical trials evaluating minimal residual disease-adapted therapy.

Clinical trial	Patient population	Treatment scheme
UMCC 2018.056 (NCT04140162)	Phase II study with MRD-driven adaptive strategy in treatment for newly diagnosed MM with upfront daratumumab-based therapy	This phase II trial will test whether the combination of DaraRd as induction therapy, followed by DRVd consolidation therapy, if needed, will result in more patients achieving MRD-negative status, relative to the standard of care. Consolidation therapy will be administered only to those patients with MRD-positive status after induction therapy.
MIDAS (NCT04934475)	Phase III clinical trials in newly diagnosed MM patients	IFM 2020-02 will enroll patients eligible for ASCT aged <66 years. All patients will receive induction based on 6 cycles (28-day) of Isa-KRd, in order to achieve deep responses and high MRD negativity rates. Patients will be classified at diagnosis according to cytogenetics (standard *vs.* high-risk cytogenetics defined by the LP score including 17p deletion, t(4;14), del(1p32), gain 1q, trisomy 21 and trisomy 5.
PERSEUS (NCT03710603)	Phase III clinical trial daratumumab, VELCADE (bortezomib), lenalidomide and dexamethasone compared to VELCADE, lenalidomide and dexamethasone in subjects with previously untreated MM	A phase II study comparing D-VRd *vs.* VRd in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy. MRD-negative subjects will stop daratumumab after sustained MRD negativity for 12 months and after a min. of 24 months of maintenance. Daratumumab should be restarted at recurrence of MRD or confirmed loss of CR without disease progression.
DRAMMATIC (NCT04071457)	Phase III clinical trial lenalidomide +/- daratumumab/rHuPh20 as post-ASCT maintenance for MM w/MRD to direct therapy duration (DRAMMATIC)	In this trial, patients who received HDC-SCT are randomized between lenalidomide for 2 years and lenalidomide + daratumumab. After 2 years of maintenance, MRD is assessed to guide further therapy. MRD-positive patients will continue with the assigned treatment. MRD-negative patients will be further randomized to either continue or discontinue the assigned treatment.
EMN20 (NCT04096066)	Phase III clinical trial. A trial that compares two treatments in newly diagnosed myeloma patients not eligible for transplant (KRd *vs.* Rd)	This protocol is a randomized, multicenter study designed to determine the MRD negativity and the PFS of KRd treatment regimen. Patients will be randomized in a 1:1 ratio to receive KRd (Arm A) or Rd (Arm B). Patients will be stratified basing on ISS and fitness status using a web-based procedure completely concealed to study participants. Patients will be treated until disease progression or intolerance to the therapy. The only exception is for patients enrolled in KRd arm who achieve at least a VGPR during the 1st year of treatment and in sustained MRD negativity (MRD negative at least at 10-5 after 1 and 2 years of therapy): these patients will stop carfilzomib administration after 2 years, whereas treatment with lenalidomide and dexamethasone will be continued.
MASTER-2 (NCT05231629)	Phase II clinical trial. Sequential therapy in MM guided by MRD assessments (MASTER-2)	This research study will determine the proportion of patients with lowest MRD response obtainable after receiving 6 cycles of study treatment. MRD is MM cells below the level of 1 cancer cell out of 100,000 in the BM. For patients who become MRD 'negative' (i.e. less than 1 cancer cell out of 100,000) at the end of 6 cycles of therapy, this study will evaluate if that good response can be maintained with 3 additional cycles of treatment instead of use of ASCT. For patients who are MRD 'positive' at the end of 6 cycles of therapy, this study will answer whether more patients can become and remain MRD 'negative' with ASCT plus teclistamab in combination with daratumumab when compared with patients who undergo ASCT followed by lenalidomide plus daratumumab.
RADAR (EudraCT 2019-001258-25)	Phase III clinical trial. Risk-adapted therapy directed according to response comparing treatment escalation and de-escalation strategies in NDMM suitable for stem cell transplant	All participants will receive the same initial induction treatment and during this time will have genetic tests to determine whether they have 'standard-risk' or 'high-risk' disease. Following this chemotherapy treatment participants will receive ASCT. After induction treatment participants will be allocated to a second stage treatment group based on their genetic risk, high-risk or standard-risk, and on how well the myeloma has responded to the initial treatment. Each treatment group will then receive different combinations of medication to investigate their benefit. Treatment will comprise of combinations of isatuximab, bortezomib, cyclophosphamide, lenalidomide and dexamethasone.

ASCT: autologous stem cell transplanation; BM: bone marrow; CR: complete remission; DaraRd: daratumumab + lenalidomide + dexamethasone; DRVd: daratumumab + lenalidomide + bortezomib + dexamethasone; D-Vrd: daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone; HDC: high-dose chemotherapy; IFM: Intergroupe Francophone du Myélome; Isa-KRd: KRd-isatuximab; ISS: International Staging System; KRd: carfilzomib, lenalidomide and dexamethasone; MIDAS: Minimal Residual Disease Adapted Strategy; NDMM: newly diagnosed patients with multiple myeloma (MM); PFS: progression-free survival; Rd: lenalidomide-dexamethasone; Vrd: VELCADE, lenalidomide, and dexamethasone; VGPR: very good partial response.

Cumulative incidence of MRD resurgence or progression 12 months after cessation of therapy was 4%, 0%, and 27% for patients with 0, 1, or 2 HRCA, respectively.[82] Similarly, a phase III clinical trial (GEM2012MENOS65) evaluated lenalidomide and dexamethasone maintenance with or without ixazomib in newly diagnosed myeloma patients, with treatment stopping after 24 cycles in case of BM-based MRD-negativity. Patients achieving MRD negativity after 24 months of maintenance therapy had a low progression rate (17.2%) at four years, strongly suggesting that the duration of maintenance therapy can be tailored based on MRD negativity.[87] Accordingly, data regarding achievement of MRD negativity and early relapse have been reported but not yet published in high-risk MM patients included in the CASSIOPEIA trial.[73] Although longer follow-up is needed, these trials already suggest that cessation of treatment may be feasible in patients with standard risk cytogenetics but not for patients with HRCA. Improving MRD assessment by combining BM and imaging evaluation may be more relevant in high-risk cytogenetic patients in front-line. Another important observation has been reported in a phase II study evaluating MRD dynamics during lenalidomide maintenance. Patients who lost MRD negativity were more likely to progress than patients with sustained MRD negativity (HR infinite; P<0.0001) as expected, but also and worse than patients with persistent MRD positivity (HR 5.88, 95% CI: 1.18-33.33; P=0.015) at the 2-year landmark. These data suggest that the dynamic of the disease is another very important parameter to consider when evaluating the use of MRD as a therapeutic guide.[88]

The ongoing MIDAS trial (*clinicaltrials.gov 04934475*) is designed to evaluate the role of HDC-SCT on the basis of MRD status after induction in newly diagnosed MM patients. In this trial, patients are treated with 6 cycles of quadruplet regimen induction with combined isatuximab, carfilzomib, lenalidomide and dexamethasone (Isa-KRd) and evaluated for BM-based MRD (with a threshold of 10^{-5} cells) post induction. Patients are next stratified into standard risk (MRD negativity < 10^{-5}) or high risk (MRD positivity> 10^{-5}). Patients achieving MRD negativity following induction are randomized to receive 6 additional cycles of Isa-KRd followed by maintenance or HDC-SCT, followed by 2 cycles of Isa-KRd, and maintenance with lenalidomide for three years. High-risk patients defined by MRD positivity post induction are randomly assigned to receive HDC-SCT followed by 2 cycles of Isa-KRd *versus* tandem HDC-SCT followed by isatuximab-iberdomide maintenance for three years. This ambitious trial will address whether MRD status can be used to guide therapy, and if HDC-SCT remains the gold standard in patients achieving early MRD negativity after induction.

Several other randomized clinical trials are evaluating MRD-based treatment decision. The PERSEUS trial (*clinicaltrials.gov 03710603*) will evaluate the possibility of stopping daratumumab during maintenance in patients achieving sustained MRD negativity for 12 months and after a minimum of 24 months of maintenance, and the benefit of restarting daratumumab in case of MRD conversion (from negative to positive) or confirmed loss of CR without IMWG disease progression criteria.[89] The AURIGA trial (*clinicaltrials.gov 03901963*), randomly assigns patients who have achieved VGPR but who are MRD-positive to receive daratumumab and lenalidomide *versus* lenalidomide maintenance for the primary endpoint of MRD conversion at 12 months from initiation of maintenance. The DRAMMATIC trial (*clinicaltrials.gov 04071457*) by the Southwest Oncology Group (SWOG; S1803) randomly assigns patients to receive daratumumab and lenalidomide *versus* lenalidomide maintenance post HDC-SCT. After two years of maintenance, MRD is assessed to guide further therapy. MRD positive patients will continue with the assigned treatment while MRD negative patients will be further randomized to either continue or discontinue the assigned treatment. The OPTIMUM trial *(clinicaltrials.gov 03941860*) by the Eastern Cooperative Oncology Group (ECOG; EAA171) will randomly assign MRD positive patients who are receiving lenalidomide maintenance after HDC-SCT to receive ixazomib or placebo in addition to continuing lenalidomide.

In conclusion, MRD assessment methods have significantly improved in the past two decades and allow identification of patients with deep hematologic response. BM-based methods using NGF and NGS are to date the most available, standardized, and sensitive methods. WBI includes wbMRI, and PET/CT are also very interesting, and when combined with BM MRD assessment provide better evaluation especially in the setting of high-risk cytogenetics and EMD. Achievement of MRD negativity is a very strong prognostic factor that is now an established endpoint in myeloma clinical trials. Persistent or sustained MRD negativity portends better outcome in newly diagnosed and RR disease, including after CAR T-cell therapy in myeloma and may allow discontinuation of therapy in patients without high-risk cytogenetics. Several clinical trials are currently ongoing to establish whether MRD can be used to guide therapy and to monitor disease activity.

Disclosures

No conflicts of interest to disclose.

Contributions

All authors made a significant contribution to this article. RES, NCM and KCA took part in the conception of the manuscript, in drafting, revising and critically reviewing the article, and gave final approval of the version to be published.

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