New Developments in Diagnosis, Prognosis, and Assessment of Response in Multiple Myeloma

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Abstract

Over the past few years, the management of multiple myeloma has changed. We have new guidelines regarding how to set the diagnosis, when to initiate therapy, and how to monitor treatment response. In 2014, the updated International Myeloma Working Group (IMWG) diagnostic criteria changed the definition of multiple myeloma from being a disease defined by symptoms to a disease defined by biomarkers. Today, modern combination therapies have reported up to 60% to 80% of patients reaching a complete response. As a logical and necessary step forward, investigators have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. Recent meta-analysis data show that MRD negativity is associated with longer progression-free survival and overall survival. In 2016, the updated IMWG response criteria include MRD as the deepest level of treatment response in multiple myeloma. Simultaneously, we are still quite behind in our understanding of the heterogeneous biology of multiple myeloma and its implications for therapy. Emerging DNA sequencing data show that newly diagnosed multiple myeloma patients have a broad range of mutations, which are distributed unevenly in multiple parallel subclones already present at diagnosis. To move beyond the ill-defined category of "high-risk multiple myeloma," which confers to approximately 25% of all newly diagnosed patients, prospective studies are needed to dissect tumor biology and define multiple myeloma subtypes, and, based on biology, seek to define rational therapies for individual subtypes. This article discusses novel insights and gives perspectives on diagnosis and MRD monitoring and future directions for prognosis and clinical management of multiple myeloma. *Clin Cancer Res; 22(22); 5428–33. ©2016 AACR.*

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Introduction

Driven by access to better drugs, newly diagnosed multiple myeloma patients have, on average, more than 10 years overall survival according to available population registries (1–3). In parallel with the strong drug pipeline, clinical management of multiple myeloma has changed drastically the past few years. Without a doubt, the use of modern combination therapy integrated with modern clinical management will continue to deliver substantially longer overall survival for patients with multiple myeloma in years to come (4).

In this review, we highlight key changes with regard to diagnostic criteria (5) and treatment response assessment (6), based on recently updated International Myeloma Working Group (IMWG) consensus criteria. We also cover the topic of prognosis and how to integrate that in the clinical management of multiple myeloma. Specifically, we review novel data and give perspectives on diagnosis and minimal residual disease (MRD) monitoring and future directions for prognosis and clinical management of multiple myeloma.

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Diagnosis

Going back to the 1960s, the clinical paradigm for multiple myeloma used to be watch and wait and to initiate therapy once the patient was clinically ill and suffered from symptoms. Certainly, a key limitation, at the time, was the lack of available therapies (restricted to alkylating chemotherapy and steroids; ref. 7). In that era, once the decision was made to start therapy, the clinician had few other treatment options when therapy stopped working and the disease became active again. Fortunately, the myeloma field has changed substantially, and today, many new drugs exist that have been approved for the treatment of multiple myeloma. To adapt to this new reality, in 2014, the updated IMWG diagnostic criteria changed the definition of multiple myeloma from being a disease defined by symptoms to a disease defined by biomarkers (5). Specifically, there were three biomarkers added to the former "CRAB" (hypercalcemia, renal failure, anemia, and lytic bone lesions) criteria, so now there are seven variables that can make the diagnosis. Thus, the criteria for the diagnosis of multiple myeloma requiring therapy are 10% or more plasma cells in the bone marrow, abnormal immunoglobulins in the blood and/or urine [monoclonal protein and/or free light chains (FLC)] unless the patient is nonsecretory (which is rare), and one or more of the seven listed criteria are fulfilled (Box 1). The three newly added biomarkers are (i) abnormal serum (s) FLCs defined as an abnormal sFLC ratio (involved/uninvolved sFLC) of 100 or greater and the involved sFLC being 10 mg/dL or greater; (ii) 60% or higher plasma cell infiltration of the bone marrow; and (iii) two or more focal lesions in the bone or bone marrow as defined by whole-body (or at least spine and pelvis) MRI (Box 1; ref. 5). These arbitrary cutoffs were initially reported in retrospective single-center studies, suggesting these

Box 1. Definition of multiple myeloma based on 2014 IMWG criteria

(i) Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

(ii) Any one or more of the following myeloma-defining events (which have to be attributed to the underlying plasma cell proliferative disorder):

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL/minute and/or serum creatinine > 173 μmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >2.0 g/dL below the lower limit of normal, or a hemoglobin value <10.0 g/dL
- Bone lesions: one or more osteolytic lesions on skeletal radiography (i.e., X-ray), low-dose CT, or PET/CT
- Clonal bone marrow plasma cell percentage ≥60%
- Involved/uninvolved serum-free light chain ratio ≥100, and the involved serum-free light chain concentration 10 mg/dl or higher
- Two or more focal lesions based on MRI studies of the skeleton

NOTE: Both (i) and (ii) have to be fulfilled. See details and discussion in the text regarding the above myeloma defining event variables. Adapted from ref. 5: *The Lancet Oncology*, Vol. 15, Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, e538–48, © 2014, with permission from Elsevier.

biomarkers to be associated with, on average, around 1 year for the progression from smoldering myeloma to multiple myeloma. Subsequently, smaller efforts were launched to replicate these observations, and upon review of these reports, the IMWG consensus group felt it was clinically justifiable to integrate these biomarkers into the disease definition of multiple myeloma, to have them written up by a writing committee, and to launch them as the updated IMWG diagnostic criteria for multiple myeloma requiring therapy (5).

In addition to the three biomarkers discussed above, the updated IMWG criteria included several adjustments and improvements of the definitions of the CRAB criteria. Although there are no changes to the definitions of hypercalcemia and anemia, the definitions of renal failure and lytic bone disease have been revised. Renal failure was previously defined as an increased serum creatinine >173 μmol/L (>2 mg/dL), which is a nonreliable marker. Therefore, the new definition advises clinicians to use either the Modification of Diet in Renal Disease equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in estimating glomerular filtration rate (eGFR) in patients with myeloma, but a slight preference was given to using the CKD-EPI equation (5). Unless the renal insufficiency is due to another known cause, patients with an eGFR value below 40 mL/minute and/or a serum creatinine >173 μmol/L (>2 mg/dL) are considered to fulfill the definition of renal insufficiency as part of the diagnostic criteria for multiple myeloma (Box 1; ref. 5).

Although it is well-known that X-ray has major sensitivity limitations when it comes to the detection of bone disease, in the clinical management of multiple myeloma, skeletal surveys have historically been used to identify lytic bone lesions in multiple myeloma. The revised IMWG criteria state that (i) skeletal survey, (ii) PET/CT, or (iii) low-dose CT represent valid methods, which can be used to rule out lytic bone lesions (Box 1). The definition of a lytic lesion is arbitrarily set to 5 mm or greater diameter bone destruction. As a point of reference, in routine clinical care at Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY), Landgren and colleagues implemented PET/CT as the default method to rule out lytic bone lesions in patients with plasma cell disorders. PET/CT has more than 20- to 30-times higher sensitivity than a skeletal survey (8). Another clinical way of illustrating the difference in sensitivity between the two methods comes here: In our experience, among 100 smoldering myeloma patients with a negative skeletal survey, we typically find 20 to 30 to have lytic bone lesions by PET/CT. It should be emphasized that lytic lesions are defined by the CT portion of the PET/CT, independent of whether there is PET uptake or not. In fact, the PET portion has many limitations in the setting of multiple myeloma; it is nonspecific and nonsensitive (8). For example, patients with multiple myeloma who have known lytic bone lesions may be PET negative due to slow metabolism of the myeloma cells (8). Also, positive PET uptake is commonly seen due to inflammation, degenerative joints, or other causes. Importantly, on a practical note, PET/CT is used to monitor other diseases, and increased PET SUV uptake has direct clinical impact (e.g., in the management and treatment of lymphomas). In contrast, quantification of abnormal SUV uptake is currently not part of the routine clinical management in multiple myeloma. Instead, the clinical focus is dependent on the CT portion's ability to identify or rule out lytic bone lesions. Although this may sound trivial, due to lack of communication between physicians managing patients with plasma cell disorders and physicians reading PET/CT results, in many clinics around the world, the full imaging reports from PET/CT are done by nuclear medicine specialists and not radiologists. Consequently, in these instances, the PET/CT report reflects mostly (only) SUV uptake by the PET tracer, and the value of the more sensitive CT portion (compared with skeletal survey) might be missed for the purpose of detecting early bone disease. Therefore, clinicians seeing patients with plasma cell disorders need to be aware of these facts and, if needed, should be encouraged to seek contact with their corresponding imaging colleagues to ensure that the PET/CT assessments and reports are optimized for the detection of lytic bone lesions. For example, in centers where nuclear medicine specialists are leading the work with PET/CT, two parallel reports can be generated for myeloma PET/CT evaluations: one by a radiologist (CT portion) and one by a nuclear medicine specialist (PET portion).

On a clinical note, we would like to add further perspectives and discuss more details on the new biomarkers that were added to the IMWG diagnostic criteria. Specifically, we would like to address the issue with 60% or more plasma cell infiltration of the bone marrow. Typically, patients with such high percentage of

infiltration of the bone marrow have other abnormalities, such as anemia, pain, and perhaps lytic bone lesions. However, there are cases where the plasma cell infiltration is high in the absence of other criteria. It should be stressed that there are different ways to determine the plasma cell percentage in the bone marrow. In clinical practice, typically, there are three measures of plasma cell percentage of the bone marrow reported to the clinician: (i) plasma cell percentage determined by counting cells on a core biopsy with immunohistochemical staining with CD138 antibody, (ii) plasma cell percentage determined by counting cells on an aspirate smear, and (iii) plasma cell percentage as determined by the flow cytometry machine. Many times, medical fellows ask in clinic, "Which plasma cell percentage of the bone marrow is correct?" The correct answer is: "The highest number, which is typically the plasma cell percentage determined by counting cells on a core biopsy with immunohistochemical staining by CD138." This is important, as the results are highly different between these methods. In our clinical experience, if a core biopsy immunohistochemically stained by CD138 shows 60%, the typical aspirate smear shows about 30% (due to blood contamination and underestimation), and the flow cytometry machine may show in the range of 2% plasma cells (due to blood contamination and cell lysis). The correct answer in this case is 60% plasma cell infiltration of the bone marrow. It should be mentioned that CD138 staining requires more specialized training than regular hematoxylin and eosin (H&E) staining; H&E typically gives a lower plasma cell count than CD138 staining. In unclear cases, a second opinion by a specialized myeloma center is preferable to ensure optimal patient care.

Finally, we would like to give a few final comments on MRI assessment of the skeleton. The original study by Hillengass and colleagues used whole-body MRI in a series of 149 patients with smoldering myeloma, and they showed that, among those with two or more focal lesions ($n = 23/149$, 15%) in the bone or bone marrow, 12 of 23 (50%) had progression to multiple myeloma within 13 months and 16 of 23 (70%) had progression to multiple myeloma within 2 years (9). To expand on these findings, a Greek study group assessed 67 patients with smoldering myeloma with MRI of the spine and the pelvis; 9 of 67 (14%) patients had two or more focal lesions, and all 9 had progression to multiple myeloma within 4 years (10). On the basis of these data, the IMWG consensus panel decided to use MRI as a biomarker for the diagnosis of multiple myeloma (5). Although the IMWG criteria allow either of the two approaches (due to differences in availability of MRI around the world), several clinical questions remain. For example, is it necessary with whole-body MRI, or is spine and pelvis sufficient? In the study by Hillengass and colleagues (9), 90% of the focal lesions were observed in the spine and pelvis; thus, 10% may be missed if whole-body MRI is not conducted. Also, a common clinical question pertains to the use of PET/CT versus MRI: Is there added value in doing both, or can MRI be skipped? The correct answer is: "There are not enough data to give a definitive answer; the IMWG guideline states that both methods shall be done (5)." Imaging wise, MRI is a better method to assess soft tissue (such as bone marrow), and CT is better for hard tissue (such as bone). In clinical practice at MSKCC, Landgren and colleagues order PET/CT first, and if negative for lytic bone lesions, they order whole-body MRI to rule out focal bone marrow areas. If the PET/CT is positive, typically, they do not proceed with MRI as the patient already fulfills the criteria for having multiple myeloma. It should be stressed that there is no universal definition of a "focal bone marrow lesion by MRI" in the literature. Future IMWG guidelines will benefit from involving imaging specialists in addition to myeloma specialists.

Although the IMWG diagnostic criteria are not perfect, the intent and the implications of the updated version are to facilitate earlier detection and earlier initiation of therapy with the aim of improving overall survival in multiple myeloma. Indeed, population-based data support earlier detection and initiation of therapy in multiple myeloma (11).

Prognosis

It is probably fair to say that the myeloma field is quite behind when it comes to our understanding of the heterogeneous biology of multiple myeloma and its implications for therapy. Emerging DNA sequencing data show massive genetic heterogeneity across and within given multiple myeloma patients (12). It has been found that, on average, a patient with newly diagnosed multiple myeloma has mutations in a large number of genes, and these mutations are unevenly distributed in parallel subclones already present at diagnosis (12, 13). Despite all success for the majority of multiple myeloma patients, today, approximately 25% of all newly diagnosed patients live less than 3 years (14). Although only limited data are available at this time, this is probably not true in the setting of our current best therapies, as some of the formerly considered "high-risk myeloma" cases do quite well with modern therapy (15). This phenomenon illustrates the fact that poor prognosis always has to be viewed in the light of a given therapy. Clearly, it seems reasonable to believe that certain subtypes within the former group of clinical high-risk myeloma cases will be considered standard risk as newer therapies become better and better. On the other hand, it is frustrating that a nontrivial proportion of patients with newly diagnosed multiple myeloma continues to experience treatment failure. In our opinion, a key task for the field is to move beyond the ill-defined clinical category of high-risk myeloma, which presumably contains several biological subtypes. To make this happen, prospective studies are needed to dissect tumor biology and define multiple myeloma subtypes, and, based on biological insights, seek to develop rational therapies for individual subtypes. Finally, beyond a better molecular definition of multiple myeloma patients based on DNA sequencing, gene expression analysis based on RNA expression has information on activation of genes and pathways involving several genes independent of mutational status (16). Future integrated analyses of DNA and RNA signatures will allow further characterization of biology and prognosis in relation to given therapies.

Assessment of Response

At the beginning of the 21st century, multiple myeloma had an average overall survival of about 3 years (4). Around that time, three drugs (bortezomib, lenalidomide, and thalidomide) were introduced for the treatment of multiple myeloma, and in 2012, the FDA granted accelerated approval to carfilzomib. The FDA approved 14 new drugs for the treatment of cancer in 2015; four of these were approved for the treatment of myeloma (panobinostat, daratumumab, elotuzumab, and ixazomib; ref. 5). In 2015 and 2016, expanded label indications were approved by the FDA for lenalidomide and carfilzomib, respectively (5). The increased availability of highly effective targeted agents with limited overlapping toxicities has shifted the therapeutic paradigm from

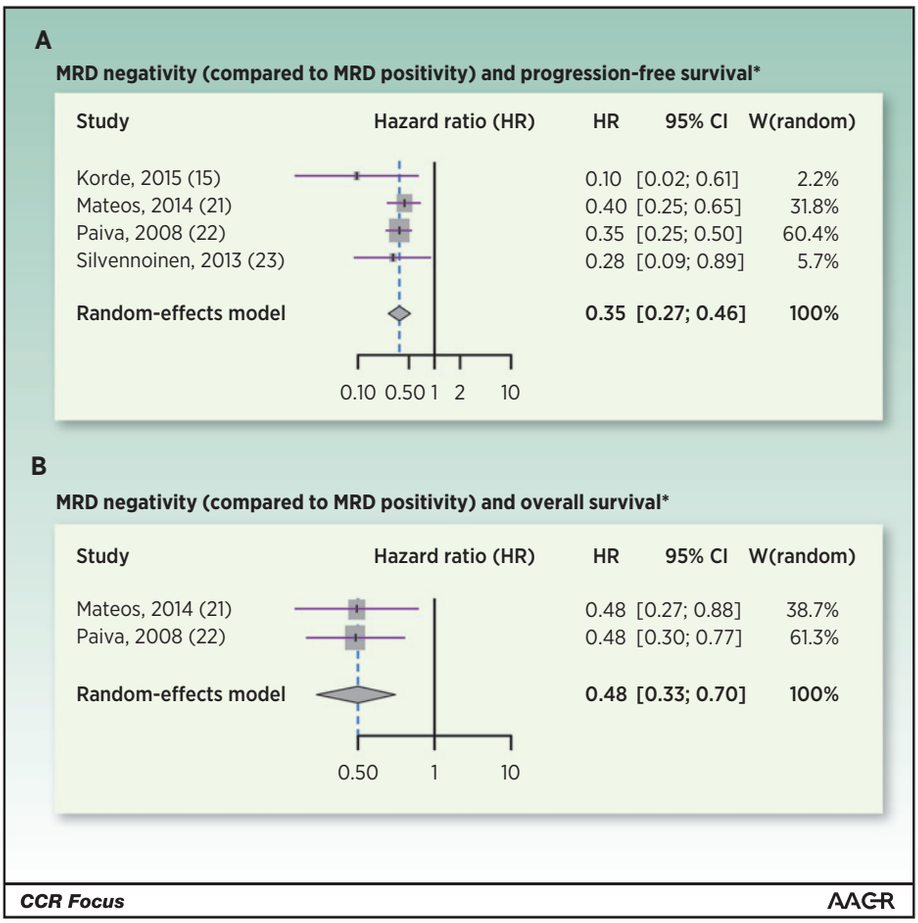

Figure 1.
MRD negativity associated with longer progression-free survival (**A**) and overall survival (**B**) in newly diagnosed multiple myeloma patients. Four studies with information on MRD status and HRs for progression-free survival were included in the final analysis (15, 21–23); three studies had information on overall survival (15, 21, 22); however, one study had no deaths during the original follow-up window (15), so two studies provided HRs for overall survival. CI, confidence interval. *, A lower HR indicates decreased risk for each survival endpoint (i.e., MRD negativity associated with lower risk of progression and lower risk of dying). Reprinted from Landgren and Giralt (4).

palliative two-drug combinations toward the use of modern, effective three-drug combination strategies (17). Reflective of the fast moving field, studies are already ongoing to evaluate modern four-drug combinations, including mAbs in combination with proteasome inhibitors, immunomodulatory drugs, and low-dose steroids (18). Clinical trials evaluating combination regimens incorporating recently approved agents have shown that patients across the myeloma disease continuum are able to achieve deep and durable responses, including MRD negativity, and improved patient outcomes (17). As a logical and necessary step forward, investigators have explored strategies to detect MRD and its correlation with clinical outcomes (19). Indeed, recent meta-analysis data show that MRD negativity is associated with longer progression-free survival and overall survival (20). In brief, this meta-analysis including published clinical trials of patients with newly diagnosed multiple myeloma was recently undertaken. The study showed that MRD negativity is associated with longer progression-free survival [hazard ratio (HR) = 0.35; $P < 0.001$] and overall survival (HR = 0.48; $P < 0.001$; ref. 20), supportive of MRD becoming a regulatory endpoint for drug approval in newly diagnosed multiple myeloma (Fig. 1). Criteria for the definition of MRD negativity were not established until 2016 (6), so among the four studies included in the main analysis (15, 21–23), three used multiparameter flow cytometry (15, 21, 22) and one used allele-specific quantitative PCR (23), both with a sensitivity of at least 1 in 10,000 cells (10^{-4}) to determine MRD status (17). In the past few years, several assay platforms have been launched to determine MRD status in patients with multiple myeloma. The two main assay platforms are multiparameter flow cytometry based and molecular based (deep DNA sequencing of VDJ region). Currently, the flow cytometry–based platform is more easily available in clinical settings, given that most institutions have access to modern flow cytometry machines; however, there is inherent variability due to observer variability, differences in the use of antibodies, and procedures regarding sample preparation (17). Once molecular-based assays become more easily available, they will likely play a key role in MRD assessment given their high degree of reproducibility and their higher sensitivity (17). Future studies will guide the evolution of MRD assays in multiple myeloma. To harmonize procedures in this current era of available assays and to ensure that MRD status has the same meaning across studies, the IMWG recently revised the response criteria for myeloma and included MRD negativity as the highest degree of response to treatment (6). On the basis of the 2016 IMWG criteria, MRD negativity can be defined by either multiparameter flow cytometry–based or molecular-based assays with a sensitivity of at least 1 in 100,000 cells (10^{-5}) to determine MRD status, and MRD status shall only be determined in patients who have achieved a conventional complete response (Box 2; ref. 6). Moving forward, as better and better drugs become available for the treatment of multiple myeloma, ironically, traditional regulatory endpoints (i.e., overall survival and progression-free

Box 2. Definition of MRD negativity based on 2016 IMWG criteria

MRD negativity

- Requires complete response
- Requires absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with a minimum sensitivity of 1 in 10^5 nucleated cells or higher (i.e., 10^{-5} sensitivity)[a]

NOTE: Adapted from ref. 6: *The Lancet Oncology*, Vol. 17, Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al., International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328–46, © 2016, with permission from Elsevier.

[a]Based on flow cytometry or next-generation sequencing (such as the EuroFlow standard operation procedure for MRD detection in multiple myeloma, or other validated equivalent methods; LymphoSIGHT, or other validated equivalent method).

survival) will become key barriers to drug development (19). As pointed out in the literature, there is an urgent need for reliable surrogate regulatory endpoints for drug approval (24, 25). Indeed, Gormley and colleagues, from the FDA, recently published an article on regulatory perspectives on MRD testing in multiple myeloma (26). In their article, they concluded that MRD assessment in multiple myeloma has the potential to become a surrogate clinical endpoint that could be used to support regulatory purposes for drug review (26). As stated by Gormley and colleagues, standardization of MRD testing and consensus within the multiple myeloma community as to the role of MRD and possible incorporation into the response criteria will be integral steps toward this end (26). The FDA has emphasized the importance of future meetings to facilitate a consensus process in the United States and expressed its interest in reviewing both testing protocols of MRD assays and clinical protocols incorporating MRD (26). In this context, the results from the meta-analysis play an important role, as they provide scientific evidence on the impact of MRD negativity as a strong predictor of longer progression-free survival and overall survival in newly diagnosed multiple myeloma (20). The findings are supportive of MRD assessment becoming a surrogate clinical endpoint that could be used to support regulatory purposes for drug review in multiple myeloma (26). In addition to the results from this meta-analysis, prospective clinical studies are ongoing and will further confirm and expand on these findings (20).

Future Directions

The myeloma community has made major progress in a short period. The average patient with newly diagnosed multiple myeloma has more than 10 years of overall survival today (1), and patients diagnosed in 2016 might have, perhaps, 15 or 20 years, given the increased access to newer drugs. The reason there is uncertainty on the projected overall survival is simply due to the lack of long-term follow-up data based on newer combination therapies. Indeed, we have to wait another 10 to 20 years to document the progress we have made. In the meantime, we need to improve our understanding of the biology of multiple myeloma. Overall, we need to move beyond the ill-defined category of high-risk multiple myeloma, which historically refers to 1 in 4 of all newly diagnosed patients (14). We need to develop prospective studies to dissect tumor biology. Specifically, treating patients with the best available therapies, and, in parallel, running modern molecular profiling, will allow us to define multiple myeloma subtypes. With such knowledge, hopefully, we will be able to define rational therapies for individual subtypes based on biology. In our opinion, such efforts are urgently needed to advance the field.

Also, continued work focusing on MRD is important to advance the field. To support the FDA to acknowledge MRD negativity as a regulatory endpoint (20), concerted efforts are needed, including large clinical trials capturing both MRD status and clinical outcomes (i.e., progression-free survival). Clinical trials have to be designed in a manner where all patients reaching complete response will be tested for MRD status, the MRD assay is done in a uniform way within the given study, and clinical follow-up data will be captured for all patients. In parallel with these practical steps, we need to continue developing better MRD tests with higher sensitivity and MRD tests that ultimately can be based on peripheral blood instead of bone marrow aspirates. In our opinion, access to future blood-based MRD tests will have the potential to transform the myeloma field and open up avenues for response-driven treatment strategies, with the aim to tailor treatment for maximal efficacy and limited toxicity (4). In the future, it is possible that many patients will live with multiple myeloma inactive for a very long time and that treatment adjustments will be based on changes in biomarkers before the patient develops any symptoms (functional cure). Ideally, an extended deep MRD negativity has the potential to be the pathway to full (operational) cure, at least in some patients. More hard work is needed to ensure the field will be going in this direction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: O. Landgren, S.V. Rajkumar
Development of methodology: O. Landgren
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O. Landgren
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O. Landgren
Writing, review, and/or revision of the manuscript: O. Landgren, S.V. Rajkumar
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O. Landgren
Study supervision: O. Landgren, S.V. Rajkumar

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