Predicting Outcomes and Monitoring Disease in Patients With Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a clonal plasma cell dyscrasia and the most common form of primary bone marrow cancer. Nearly 35,000 new cases of MM are diagnosed in the United States each year. MM is a slowly progressive illness that remains incurable. The median survival for patients with MM is approximately 7 years, during which these patients suffer substantial morbidity. Despite the introduction of new drugs and immune-based therapies, many patients unfortunately relapse and require further therapies. Therefore, it is becoming increasingly important to be able to accurately and quickly determine changes in a patient's clinical status. Assessments of monoclonal protein and serum free light chain levels are the most common tests now available for monitoring patients with MM; however, these assays have several drawbacks. Modern radiologic techniques such as positron emission tomography and computed tomography are better than standard radiographs but are costly and cumbersome. Serum B-cell maturation antigen is a new biomarker for both the diagnosis and prognosis of MM. Assessment of measurable residual disease is becoming an important endpoint. The creation of better ways to predict outcomes and promptly and accurately monitor changes for patients with MM should lead to improved quality of life and longer survival.

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy of monoclonal plasma cells that accounted for an estimated 35,000 new cases (1% of all new cancer cases) and 13,000 deaths in the United States in 2022.[1] Current treatment regimens consist of proteasome inhibitors such as bortezomib, carfilzomib (Kyprolis, Amgen), and ixazomib (Ninlaro, Millennium/Takeda Oncology) and immunomodulatory drugs such as lenalidomide, thalidomide, and pomalidomide (Pomalyst, Celgene). In recent years, newer and more effective

drugs have become available for the treatment of patients with MM, including the monoclonal antibodies daratumumab (Darzalex, Janssen Biotech), isatuximab (Sarclisa, Sanofi Genzyme), and elotuzumab (Empliciti, Bristol Myers Squibb); the bispecific antibody teclistamab (Tecvayli, Janssen Biotech); chimeric antigen receptor T-cell therapies such as idecabtagene vicleucel (Abecma, Bristol Myers Squibb) and ciltacabtagene autoleucel (Carvykti); and the selective inhibitor of nuclear export selinexor (Xpovio, Karyopharm). These newer agents have been evaluated alone and in combination with older agents, rapidly increasing the number of therapeutic options available to patients with MM. The clinical course of MM is variable, and predicting each patient's outcome is difficult with currently available tools. However, it is important to make more effective treatment decisions. Therefore, we must develop more effective methods and tools to characterize and follow these patients. We also must find ways to quickly determine changes in patients' clinical status so that new treatments can be initiated sooner.

International Staging System

The International Staging System (ISS) and the Revised ISS (R-ISS) are the 2 most widely used prognostic staging systems for MM. When the ISS was created, it was based on levels of serum albumin and β2-microglobulin. Avet-Loiseau and colleagues have presented data demonstrating that genetic abnormalities, including high-risk cytogenetic features such as del(13), t(11;14), t(4;14), hyperdiploidy, MYC translocations, and del(17p), and lactate dehydrogenase (LDH) levels possess prognostic significance independent of the ISS.[2,4] The International Myeloma Working Group (IMWG) changed its staging criteria in 2016 to include the ISS stage, cytogenetic characteristics, and LDH levels as a result of their findings.[3] The new revised system is known as the R-ISS.[3-5]

The R-ISS has several limitations. The study establishing this newer staging system only included patients enrolled in experimental trials, and 65% of them were younger than 65 years, whereas the average age of patients at diagnosis of MM is 70 years.[6] Information about chromosome 1 abnormalities was not collected in all trials, leading to this important prognostic parameter being omitted from the R-ISS staging.[5] Also, the lack of interlaboratory standardization of fluorescence in situ hybridization (FISH) analysis and inconsistent cutoffs for LDH levels were additional limitations of the modified staging system.[5] Studies have shown that additional prognostic factors could improve the prediction of survival[7,8] and that acquired chromosomal transformations could change the predictive capabilities of the ISS.[9,10] Despite some of these limitations, ISS and R-ISS are still the most frequently used staging systems to determine outcomes in patients recently diagnosed with MM.

The European Myeloma Network developed the Second Revision of the International Staging System (R2-ISS) for predicting overall survival (OS) in patients with MM.[11] The R2-ISS includes the prognostic factor 1q gain or amplification, resulting in better stratification of a large group of patients with intermediate-risk, newly diagnosed MM.[11] By incorporating genetic and molecular factors, including cytogenetic abnormalities and serum markers, the R2-ISS enhances the accuracy of assessing disease progression and prognosis.

Monoclonal Protein

Although baseline levels of monoclonal immunoglobulins in the serum and 24-hour urine specimens do not predict survival, these tests remain the gold standard for monitoring the patient's response to therapy. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) can recognize and quantify monoclonal immunoglobulin as an M spike.[12,13] After effective treatment, the monoclonal (M)-protein concentration is reduced as monoclonal antibody–producing malignant clonal plasma cells are eliminated, leading to a reduction in the levels of circulating M proteins.[14] SPEP, UPEP, and/or immunofixation electrophoresis are frequently used to detect these changes in M-protein levels, and can be used to determine whether the M protein becomes undetectable. Although these methods work well for many patients with MM, it is difficult to monitor individuals who have oligosecretory or nonsecretory disease.[15] Because the levels of the paraprotein are either low or undetectable among individuals with oligosecretory or nonsecretory forms of the disease, respectively, assessing M-protein levels is not feasible. In fact, 55% of patients (27/49) were not able to be assessed owing to having low amounts of the protein.[16] Another limitation of using serum M protein to monitor patients with MM is that it has a long half-life (approximately 21 days[17]), so the levels change very slowly. This limits the usefulness of M-protein measurement to detect rapid changes in disease status. The delay in changes in serum M-protein levels during treatment can also be problematic when the effects of new therapies for MM often need to be assessed quickly.[15] For patients receiving active treatment, these tests are often carried out monthly. This may pose a problem for patients who are experiencing an increase in these markers but do not yet meet the criteria for disease progression according to the IMWG criteria. This situation poses a challenge because these patients may be kept on a treatment regimen that is no longer appropriate for their worsening disease. In

addition, the use of humanized immunoglobulin G kappa (IgGκ) monoclonal antibodies to treat patients with IgGκ MM may result in detectable M protein of the same type as the MM patient's M protein, which when present at low levels can be misinterpreted as evidence of residual disease, a false-positive test result.[18] These limitations emphasize the need for integrating M-protein measurements with complementary diagnostic tools to overcome their shortcomings and provide a more comprehensive evaluation of MM.

Serum Free Light Chain

Since 2001, when polyclonal nephelometric assays became commercially available, it has been possible to measure serum free light chains (sFLCs) in a patient's blood.[19] Because of its simplicity and higher sensitivity, this approach has been proven to be a better alternative than the collection of 24-hour urine for the determination of paraprotein levels. Previously, clinicians relied on urine samples to monitor patients with light chain MM over a 24-hour period—an approach that often produced inaccurate results for multiple reasons, including the lack of urine collection for the entire 24-hour period.[20,21] Studies have also demonstrated that sFLC analysis considerably increases sensitivity when monitoring patients with MM who have residual disease.[22] Owing to their short half-life (2-6 hours), sFLCs have been recognized as having the potential to enable early monitoring for the determination of disease progression.[23,24] The latest IMWG recommendations suggest the use of sFLC assays in diagnostic screening panels and that the sFLC be used as a "biomarker of malignancy" (a difference of ≥100 mg/L between involved and uninvolved sFLCs) to identify the existence of MM in the absence of other measurable M proteins.[25] According to Moustafa and colleagues, normalization of the sFLC ratio significantly improves the predictive value of the monitoring of progression-free survival (PFS) and OS for patients with MM.[26]

Several factors limit the clinical utility of monitoring sFLC among patients with MM. Many patients do not have sufficiently elevated levels of sFLCs to make monitoring useful, so a significant proportion of subjects in whom this test can be used for a clinical evaluation of MM are excluded. Dejoie and colleagues found that sFLC testing revealed detectable levels in 98 of 157 patients (62%) with MM and intact immunoglobulin.[27] Patients with renal failure have blood FLC levels that can rise 20- to 30-fold, making the sFLC test frequently inaccurate owing to antigenic overload.[28]

According to the most current IMWG update, the sFLC test should only be used to evaluate response when both the serum and urine M-component levels are considered unevaluable. Despite this recommendation, most clinicians do not track 24-hour urine M-protein levels on a regular basis.

Specifically, a complete response (CR), according to the IMWG panel, is defined as the absence of M protein in the serum and urine, normalization of the sFLC ratio, and the presence of less than 5% clonal plasma cells in the bone marrow (BM). Stringent CR is defined as meeting the same criteria, but with the BM showing absence of detectable plasma cells using immunohistochemical or flow cytometric analysis. Recently, a more sensitive measurable residual disease (MRD)-based negative CR has been defined (see below).[29] A partial response (PR) is indicated by a reduction of 50% in the difference between involved and uninvolved sFLC levels.

Perhaps the most important limitation of evaluating sFLC is the lack of a standard way to analyze the data and assay in terms of technique and reagents, resulting in inconsistent assay interpretation.[30,31] Tate and colleagues reported that in different reagent lots, sFLC results varied by as much as 45%, with median lot-to-lot variations of 19% and 20% for κ and λ light chains, respectively.[30] Moreover, variations in the sFLC ratios between 17% and 32% were discovered, suggesting that the findings of this test should be used to assess changes in disease status with caution. The N Latex FLC monoclonal antibody test from Siemens has also added another important issue since its creation in 2011: nonequivalence. Two separate groups have shown that the findings of 2 distinct sFLC tests (the N Latex FLC and the Freelite from Thermo Fisher Scientific) vary with the testing platform, and that the 2 procedures are comparable but not equivalent.[32,33] This vast range of variance has prompted Tate and colleagues to urge for an international standard that would apply to all laboratories and ensure that values are consistent.

The Hevylite automated serum heavy/light chain (HLC) immunoassay developed by Thermo Fisher Scientific can independently assess the intact immunoglobulin of individual light chain types and κ/λ ratios. It has the capability to determine clonality based on these measurements.[34] In a study conducted by Michallet and colleagues, it was demonstrated that HLC immunoassays exhibited higher sensitivity compared with the conventional electrophoretic technique when stratifying patients who achieved a partial or better response, including PR, very good PR, or CR. In addition, a retrospective study has shown that normalization of HLC ratios predicts a longer PFS.[35]

The benefits and drawbacks of both the serum FLC and HLC assays suggest that the search for more reliable biomarkers must continue if a rapid and accurate method of evaluating a patient's response to MM therapy is to be achieved.

Positron Emission Tomography/Computed Tomography and Magnetic Resonance Imaging

Medical imaging has played an important role in the diagnosis and initial staging of MM, and in differentiating it from other plasma cell dyscrasias. Positron emission tomography (PET), which is very sensitive for the identification of isolated localized medullary lesions, is used in addition to computed tomography (CT) to examine bone lesions. Moreover, initial staging and continued monitoring of nonsecretory MM have also been done using PET/CT scans.[36,37] Many studies have shown that PET/CT scan evaluation has greater sensitivity than traditional radiography for identifying localized bone lesions.[38,39] PET/CT testing has improved with the use of radioactive tracers such as ^{18}F-fluorodeoxyglucose. This makes it feasible to distinguish between active and dormant lesions, which is particularly helpful when monitoring for potential recurrence following the start of therapy for MM.[40] Although it has been demonstrated that PET/CT-based approaches have a high level of sensitivity and specificity, and are crucial for determining prognosis in MM, it is still an expensive and somewhat inconvenient imaging procedure.

Another radiologic technique used to detect bone lesions and bone involvement among patients with MM is magnetic resonance imaging (MRI).[41] MRI is superior at identifying diffuse disease, although it is presently agreed that PET/CT and MRI are equally effective at detecting focal lesions.[41-43] In a recent study, Moreau and colleagues showed that 95% of patients had positive MRI results and 91% had positive PET/CT results at the time of diagnosis.[44] As the IMWG has stated, these results suggest that the 2 approaches are complementary for determining response and are equally effective at identifying bone lesions at diagnosis.[45,25] However, the results of this trial should be evaluated cautiously owing to the limited sample size, and it should be remembered that normalization of MRI abnormalities following 3 cycles of treatment and prior maintenance therapy was not predictive of PFS or OS.[44] Notably, whole-body MRI allows evaluation of bone lesions without the use of radioactivity, in contrast to PET/CT scans.[46]

Bone Marrow Examination

BM examination continues to be the cornerstone for establishing the diagnosis of MM.[47] Its results are utilized to distinguish between individuals with MM and those with plasma cell dyscrasia not requiring therapy, namely monoclonal gammopathy of undetermined significance (MGUS). Core biopsy samples are often examined for morphologic signs of MM, and immunophenotypic techniques are used to quantify plasma cell infiltration.[37] The most recent consensus statement from the IMWG regarding the monitoring of MM states that determination of BM plasma cell percentage for diagnosis is based on either conventional BM aspiration or biopsy; however, accurate measurement of tumor burden is preferably derived from a core biopsy specimen.[25]

The typical aspirate smear tends to underestimate the degree of plasmacytosis owing to differences in the level of blood contamination; sampling variability resulting from focal disease distribution also limits its utility. BM biopsy, which has long been considered the most accurate method of measuring plasma cell infiltration, is not without its limitations. The immunohistochemically stained trephine biopsy samples frequently exhibit more malignant plasma cell infiltration than the equivalent aspirate samples.[38-40,48] Wei and colleagues[49] reported that 25% of the patients sampled would have been misclassified as having less extensive disease if results from the examination of aspirate smears had been used alone rather than concurrently analyzed with results from the examination of CD138-stained trephine samples. In the past decade, CD138 immunohistochemical staining of a trephine biopsy section has been repeatedly validated as a superior method of identifying malignant myeloma cells[50-52] and has been widely adopted to determine the percentage of malignant plasma cells in the BM.

FISH, Cytogenetics, and MM Genes

MM is characterized by a variety of cytogenetic abnormalities that contribute to the disease's pathogenesis and clinical heterogeneity. FISH is the primary method used to identify these abnormalities, including t(4;14), t(11;14), t(14;16), t(14;20), del(17p), and del(13q). These genetic abnormalities are associated with distinct clinical features and outcomes in MM. For example, t(4;14) and del(17p) are associated with poor prognosis and resistance to standard therapies. Patients whose malignant cells show the t(11;14) marker are responsive to treatment with the B-cell lymphoma 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie/Genentech).[53] FISH analysis can detect chromosomal abnormalities in MM cells with high sensitivity and specificity. In one study, it was able to identify genetic abnormalities in 89% of patients with newly diagnosed MM and 97% of patients with relapsed or refractory MM.[54]

The traditional FISH method was compared with a newer technique called plasma cell-specific cytoplasmic immunoglobulin FISH (cIg-FISH), which is designed to detect chromosomal abnormalities specific to plasma cells. The authors analyzed BM samples from 134

patients and found that cIg-FISH was able to identify a higher number of chromosomal abnormalities than traditional FISH.[55] The cIg-FISH assay detected genetic abnormalities in 90% of patients, whereas conventional FISH detected abnormalities in only 76% of patients.[55] Patients with smoldering disease and abnormal cIg-FISH results had a higher risk of progression to active MM than patients with normal cIg-FISH results, suggesting that the cIg-FISH assay may be a more sensitive and accurate method for detecting genetic abnormalities in plasma cell neoplasms.

Recurrent mutations in *KRAS*, *NRAS*, and *BRAF* have been identified in MM and are associated with worse OS.[56] *TP53* mutations are also associated with a worse prognosis among patients with MM, suggesting that TP53 may be a potential therapeutic target.[57] Other genes that have been identified as playing a role in MM include *FGFR3*, *DIS3*, and *WHSC1*. These genes have been found to be recurrently mutated or overexpressed in MM.[58] Overall, the identification of specific genes involved in the pathogenesis of MM has led to the development of targeted therapies and improved risk stratification for patients with this disease.

Measurable Residual Disease

Novel and more sensitive primary endpoints for treatment outcomes have become a focus of myeloma research recently as treatments have improved so that the potentially increasingly curative profile of MM therapies can be better evaluated.[59] Reservoirs of low levels of MRD are thought to be the cause of eventual relapse for patients with MM. Detection of MRD is being used to predict the outcomes of patients with hematologic malignancies such as MM. By monitoring MRD levels over time, physicians can track disease progression, evaluate the effectiveness of treatments, and make informed decisions about further therapeutic interventions.[60] MRD is becoming a valuable tool for tailoring treatment plans to the individual patient's needs and improving OS rates.[61] The ideal test for evaluating MRD should have several relevant characteristics, including a high degree of applicability, sensitivity, specificity, feasibility, accessibility, and reproducibility. To date, currently available approaches have not achieved these goals. First and foremost, the standardization of MRD assays is crucial for ensuring consistent and reliable results across different laboratories. Currently, there is a lack of uniformity in assay methodologies, sensitivity thresholds, and interpretation criteria. This variability can significantly impact the reliability and comparability of MRD data, hindering its widespread clinical applicability. Moreover, the clinical significance and optimal utilization of MRD measurements in treatment decision-making are still evolving areas of research. Although MRD negativity is generally associated with improved outcomes, the precise threshold and timing for intervention based on MRD results remain uncertain. Determining whether to escalate or de-escalate therapy based solely on MRD status can be challenging, as the correlation between MRD levels and long-term clinical outcomes is complex and influenced by various factors. However, novel testing methodologies continue to be developed and improved to measure MRD more sensitively and accurately. The most commonly used MRD assessment methods use allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), next-generation sequencing (NGS), and multiparametric flow cytometry (MFC).

In addition, the use of circulating tumor and immune cells can also provide another minimally invasive method for risk stratification in smoldering MM.[62] Analyzing the presence and characteristics of these cells in the blood can help identify patients who are at elevated risk of progressing to active MM.[62] By incorporating this approach into clinical practice, healthcare professionals can potentially improve early detection and intervention strategies for patients with smoldering MM, leading to more personalized and effective treatment plans. Specific techniques used to assess MRD are described below.

Allele-Specific Oligonucleotide Polymerase Chain Reaction

ASO-PCR of diverse heavy chain rearrangements has been used to assess MRD status.[63,64] ASO real-time quantitative PCR (ASO-qPCR) has replaced the less-sensitive ASO-PCR, but its future clinical utility as a test for MRD status remains underwhelming. One significant shortcoming of ASO-qPCR is its failure rate. ASO-qPCR is feasible in less than 80% of patients owing to the lack of known clonal targets for amplification in the IgH locus in the remainder of individuals.[65] Additionally, ASO-qPCR requires patient-specific reagents, which greatly increases the cost of the test and the expertise needed to run it.[66] When the PETHEMA group used ASO-qPCR to determine MRD status, only 42% of samples were evaluable because of lack of clonality, unsuccessful sequencing, and/or suboptimal ASO performance.[64] However, the correlation between ASO-qPCR and multicolor flow cytometry was found to be strong when the tests were evaluated in the patients for whom MRD testing was feasible (correlation coefficient [r] for bivariate analysis; r=0.881; $P<.0001$).[67] Although MRD evaluation by ASO-qPCR is sensitive and specific, it has been found to have serious shortcomings and has been supplanted by NGS methods.

Next-Generation Sequencing

The development and refinement of NGS techniques,

such as massive parallel sequencing, will undoubtedly reshape the MM landscape. This sequencing-based method uses consensus primers to amplify and sequence all rearranged immunoglobulin gene segments present in a myeloma cell. A high degree of analytic reproducibility with the use of a specific, in-house technique has been demonstrated[68] and this fully automated technique can be implemented in any laboratory with NGS capability, minimizing variation among laboratories.

Preliminary studies suggest that NGS is a widely applicable test that is suitable in 91% of cases.[65] Additionally, these assessments have been found to identify residual disease with a sensitivity of 0.0001% (<1 in 10^6 cells) and are at least as sensitive as[65] and possibly more specific than[69-71] ASO-PCR assessments. In the future, it may be possible to use NGS methods to monitor MRD using peripheral blood samples instead of BM samples. Pilot studies have already begun, with relatively promising results.[72] In fact, recent studies suggest that peripheral blood may be a more accurate predictor of MRD than BM-derived cells.[73]

Multiparametric Flow Cytometry

The MRD measurement obtained with MFC has been identified as a possible early prognostic biomarker.[74] MFC methods originally were validated for use only among patients receiving a stem cell transplant[75]; however, their utility has expanded to include virtually all patients with MM.[76-79] Most recently, next-generation flow cytometry has been shown to improve the sensitivity and prognostic capability of both the first-generation 4- or 6-color MFC assays and the newer 8-color MFC assays.[79] The greater sensitivity of next-generation flow cytometry than conventional flow cytometric techniques has been attributed to an approach that optimizes a combination of fluorochromes and antibody reagents that increases specificity at very low levels of MRD, allowing for a greater number of cells to be evaluated. These new methods have been shown to provide a sensitive, more standard approach for MRD detection in MM, which overcomes some of the major limitations of conventional flow cytometry methods, such as lack of precision and standardization.[79]

Although improvements have been made, no standard MFC method exists. Although the IMWG has incorporated MRD status into its response criteria,[81] no consensus exists on the role of MRD status in patients who do not achieve a CR. During their validation, Flores-Montero and colleagues[79] noted that blood contamination, which has the potential to confound assay results, was present in 17 of 110 BM samples from patients with a very good PR or better, including the only 2 samples from patients with disease progression. In these cases, the authors suggested that a second BM sample might be needed—an unwelcome procedure for frail or elderly patients with MM. In a recent study conducted by Foureau and colleagues,[80] a protocol was identified that enables accurate MRD testing while maintaining the integrity of other BM examinations and minimizing patient discomfort. The researchers discovered that obtaining a BM aspirate volume of 3.6 cc was adequate to achieve a 10-million cell analytical input in 90% of cases.[80] In addition, the heterogeneous involvement of malignant plasma cells in the BM of patients with MM is a major limitation of all these MRD-related approaches.

Mass Spectrometry

Mass spectrometry (MS) is a powerful analytic technique used in proteomics research to study the expression, structure, and function of proteins. In recent years, MS-based assays have emerged as promising tools for the diagnosis, prognosis, and monitoring of MM. MS works by ionizing molecules in a sample and measuring their mass-to-charge ratios (m/z) to determine their identity and abundance.[82] In the case of M protein, serum or urine samples are first subjected to protein electrophoresis, a technique that separates proteins based on their size and charge.[83] MS detects M proteins through the unique sequence of the complementarity-determining region (CDR).[84] Each plasma cell produces a unique Ig with a specific CDR, and this CDR sequence undergoes somatic hypermutation, increasing its specificity as a protein marker for the malignant plasma cell. Peptide fragments are analyzed using MS to determine the molecular weight of each fragment, which is used to identify the specific protein from which the fragment originated. This process is known as peptide mass fingerprinting.[85] In addition to identifying the M protein, MS can also quantify the amount present in a blood sample. This is achieved by comparing the intensity of the M-protein peak to that of a known internal standard, which is added to the sample before analysis.[86] This allows for the detection of much lower levels of M protein than is possible with conventional methods.[86] This should be advantageous for early detection of disease progression among secretory patients whose M protein has become undetectable using standard testing. In support of this, a recent study shows much earlier detection of progressive disease among patients in so-called CR using this assay compared with conventional monitoring.[87] MS-based assays should also allow some patients to be monitored who have nonsecretory disease and M protein that is present but below detectable levels using conventional tests.

Matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry has been used for patients with MM. MALDI-TOF can analyze the peptide profiles of plasma samples, which allows for the

identification of disease-specific biomarkers.[88] In MM, MALDI-TOF has been used to identify other protein biomarkers that are associated with disease progression and prognosis.[89] For example, the expression levels of certain peptides derived from fibrinogen alpha chain and β2-microglobulin have been found to be predictive of disease progression and OS.[89,90]

MS-based assays have emerged as promising tools for the diagnosis, prognosis, and monitoring of MM by identifying disease-specific biomarkers and are being used to monitor treatment response. However, further research is needed to validate these assays and to optimize their clinical uses.

Other Biomarkers

Although a wide range of possible biomarkers have been proposed, only a few seem to offer clear, reliable, and consistent clinical data.[91] Serum interleukin 6 (IL-6) is a major growth factor in MM.[92] This pleiotropic cytokine[93] activates many pro-survival and antiapoptotic pathways simultaneously, affecting myeloma cells primarily through paracrine signaling from BM stromal cells, and to a lesser extent through autocrine signaling in a subset of patients.[94-96] However, IL-6 remains a questionable indicator of disease.[97] Although some groups have found that survival times were significantly shorter in patients whose IL-6 levels remained above a threshold of 7 pg/mL,[98] others were unable to find a correlation between plasma levels of this cytokine and disease activity.[99]

Patients with MM have elevated levels of sclerostin, a powerful inhibitor of Wnt signaling released by mature osteocytes in healthy bone tissue.[100,101] It has been discovered that low osteoblast function and poor survival are associated with higher blood sclerostin levels.[102] However, these results have been difficult to replicate, and other groups have been unable to detect significant differences between the sclerostin levels of patients with MM and those with MGUS or healthy donors.[103] Both age[104] and proximity to BM[105] may play a role in explaining these conflicting results.

Syndecan-1, also known as CD138, is a heparin sulfate proteoglycan that is abundant on the surface of malignant and healthy plasma cells.[106] Patients with MM have greater levels of soluble syndecan-1 than healthy donors.[107-109] Soluble levels among individuals with MM were found to be much greater in BM samples than in peripheral blood samples,[110] indicating that the more intrusive approach could produce more accurate findings. Baseline serum levels of syndecan-1 have been found to be lower among those who responded to chemotherapy than among nonresponders, but they do not predict therapeutic response or survival.[107] The results of studies evaluating soluble syndecan-1 are mixed, and further investigation is required before syndecan-1 measurement can be added to the panel of MM tests.

Measurement of levels of serum B-cell maturation antigen (sBCMA), a new protein marker used to follow patients with MM, can overcome some of the limitations of the current tests in predicting outcomes and monitoring patients with MM. BCMA (or TNFSFR17) is an extracellular protein present on the surface of mature B cells and terminally differentiated plasma cells.[111] sBCMA levels are higher among patients with active MM than among those with smoldering disease, and are higher among those with smoldering MM than among those with MGUS.[112] Among patients with smoldering MM and those with MGUS, higher levels of sBCMA predict a higher risk of transformation to active MM.[113,114] Among patients starting new treatment, baseline sBCMA levels predict both PFS and OS.[102] Changes in sBCMA levels during treatment correlate with changes in traditional MM markers,[112] but occur more rapidly.[8,111] This allows the opportunity to identify worsening disease more rapidly. Recent studies show that this protein marker can be used to follow patients with nonsecretory disease.[112] Levels of sBCMA are not impacted by renal function.[115] Further studies are needed to establish the role of sBCMA as a predictive and monitoring tool for patients with MM.

Conclusion

As patients and their treating physicians explore a growing range of treatments during the course of their illness, it is becoming increasingly important to accurately and quickly identify changes in the clinical state of patients with MM. Currently available tests for monitoring most often include periodic assessments of M-protein and sFLC levels, but the tests have several limitations. Many patients with MM do not have high enough M-protein levels to be evaluable, and the slow changes in M-protein levels postpone the identification of clinically important changes in clinical status that frequently occur. Among individuals with renal impairment, which frequently occurs in patients with MM, levels of sFLC may be difficult to interpret. These limitations may be addressed and the outcomes for patients with MM may be improved with the introduction of tests that can more rapidly and accurately identify changes in their clinical status. Modern radiologic methods, including PET/CT and MRI, have discovered lesions that are not visible on ordinary radiographs. The varied nature of myelomatous involvement within the BM, along with the use of various methods to retrieve a sample, such as aspiration compared with biopsy, makes it challenging to utilize BM examination for regularly monitoring patients with MM. These

problems are relevant when BM is used as a tissue source to determine MRD. Patients with MM are being more frequently assessed for MRD as treatments become ever more effective, so that lower levels of tumor cells remaining in patients can be identified. The multiple approaches used to assess MRD—ASO-PCR, NGS, and MFC—are becoming more reliable, but they are expensive, and their importance in clinical decision-making has not been demonstrated. The use of MS-based assays may provide another avenue to testing for minimal amounts of M protein that are not identified by currently available tests.

The creation of novel markers and methods for quicker and more accurate evaluation of changes in tumor load and degree of involvement among patients with MM will lead to many clinical advantages. First, patients will learn sooner whether therapies are working, so that they can minimize the unnecessary side effects of ineffective treatment and move on to another therapeutic option before their disease further affects them adversely. Second, it may be possible to use fewer drugs and lower doses if the markers can detect changes in clinical status within days rather than months. Physicians will add more drugs and use higher doses only if the less aggressive treatment is ineffective, thereby avoiding unnecessary side effects and costs associated with additional agents and higher doses. Third, the new biomarkers may detect changes in tumor burden quickly enough to help guide the dosing and scheduling of new drugs. For instance, analysis of serum BCMA levels has shown that during monthly immunomodulatory drug treatment, the tumor burden rises during the typical 1-week-off period,[8] suggesting that continuous treatment with these agents may be optimal. Fourth, these techniques may help determine whether patients can discontinue therapy without compromising their outcomes, and also detect patients with early disease progression who might benefit from earlier changes in their treatment. It will be crucial to produce properly thought-out studies that can offer conclusive evidence to justify the use of these markers and approaches in enhancing the outcomes of patients with MM.

Disclosures

Dr Kim has no conflicts of interest to report. Dr Berenson is a director, employee, and shareholder of ONCOtracker, Inc, a company that is involved in the commercial development of soluble BCMA as a disease marker.

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