Laboratory Measures for the Diagnosis, Clinical Management, and Evaluation of Treatment Response in Multiple Myeloma

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Abstract

Tumor markers include substances secreted by or in response to tumor cells and are measured in tissue or other body fluids. Biomarkers have been most widely used in the diagnosis and evaluation of treatment response in solid tumors, such as prostate-specific antigen (PSA) for prostate cancer and CA-125 for ovarian cancer. The use of tumor markers in hematologic malignancies has been limited. Advances in hematopathology including genetic and molecular analysis have provided insight into the pathobiology of hematologic diseases including multiple myeloma (MM). No single biomarker is known for the diagnosis or ongoing monitoring of MM; instead, laboratory measures pointing to genetic and molecular attributes provide the basis for diagnosis, staging, risk-adapted treatment selection, and ongoing evaluation of response. Clinical management guidelines recently proposed by the National Comprehensive Cancer Network (NCCN), International Myeloma Foundation (IMF), and Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) have been modified to include these attributes. Familiarity with these updates is necessary for the advanced practitioner involved in the clinical management of the patient with MM. Laboratory measures used for the diagnosis, clinical management, and evaluation of treatment response in MM will be reviewed, with current recommendations for frequency of monitoring and clinical interpretation.

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Multiple myeloma (MM) is a plasma cell neoplasm characterized by malignant transformation and clonal expansion of mature plasma cells resulting in an overproduction of plasma cell proteins (immunoglobulins). Risk factors for the disease are poorly understood, but there is a higher incidence in older adults, males, and African Americans, with a decreased incidence in the Asian population (Jemal et al., 2009). Multiple myeloma is clinically and pathologically heterogeneous, resulting in a wide variability in response to treatment and survival. Death rates have decreased by 11.3% in women and 7.25% in men be-

Table 1. High-risk features in multiple myeloma

Cytogenetics and associated oncogenes	Other high-risk laboratory features	Cytokines implicated in multiple myeloma pathogenesis	Additional high-risk features
Cyclin D1 t(11;14); Multiple myeloma SET domain t(4;14); C-maf t(14;16); Cyclin D3 t(6;14); mafB t(14;29); *p53* dysregulation (17p13) -13q	β_2M > 4 mg/L; Serum albumin < 3 g/dL; Nonhyperdiploid; ISS stage III; Bone marrow plasma cells > 50%	IL-6, IL-10, IL-11; Tumor necrosis factor; IGF-1 and IGF-2; Vascular endothelial growth factor	Relapse < 12 months from HSCT or first-line therapy; Preexisting complex or poorly controlled comorbidities

Note: β_2M = beta$_2$-microglobulin; HSCT = hematopoietic stem cell transplantation; IGF = insulin-like growth factor; IL = interleukin; ISS = International Staging System. Data from Avet-Loiseau et al., 2010; Kurtin, 2010; Badros, 2010; Siegel & Bilotti, 2009; Fonseca et al., 2009; Kumar et al., 2010; Tariman & Faiman, 2010.

tween 1991 and 2005 (Jemal et al., 2009). Thus, survival can vary from a few months to more than 10 years, and 20% of patients survive more than 10 years irrespective of therapy (Badros, 2010; Jemal et al., 2009; Kumar et al., 2010). High-risk attributes identified in the past decade are thought to play a role in shorter survival (Fonseca et al., 2009; Kurtin, 2010; Siegel & Bilotti, 2009).

As a result of advances in laboratory techniques and genetic analysis, patients newly diagnosed with MM can be categorized into different risk groups. This stratification assists in identifying which patients may be candidates for standard therapies, autologous stem cell transplantation, or novel therapies. Novel agents such as bortezomib (Velcade), lenalidomide (Revlimid), and thalidomide (Thalomid) used in combination with established therapies have neutralized some of these high-risk features, contributing to improved treatment outcomes (Richardson et al., 2010). The refinement of techniques and supportive care measures for autologous peripheral stem cell transplantation has also improved survival in MM (Stadtmauer, 2010). Accurate diagnosis, staging, identification of high-risk features, and ongoing monitoring for treatment response require a working knowledge of the pathobiology of the disease and associated biomarkers. Strategies used to diagnose MM, estimate risk, and evaluate treatment outcomes will be reviewed.

Bone Marrow Features and Associated MM Pathobiology

MM is a clonal plasma cell malignancy that results from a complex interaction among malignant progenitor cells (mature B lymphocytes), the bone marrow stroma, and the bone marrow microenvironment. Bone marrow stromal cells include fibroblasts, fat cells, adhesion molecules, and endothelial cells. MM cells adhere to the extracellular matrix and bone marrow stromal cells, resulting in a cascade of events including the release of cytokines from both the bone marrow stroma and the MM cells. This interaction leads to the proliferation and survival of MM cells, drug resistance in some cases, and the autocrine production of additional cytokines (Richardson et al., 2010; Siegel & Bilotti, 2009).

Cytokines are extracellular signaling molecules that activate a cascade of intracellular pathways and provide a communication mechanism between the abnormal cell and the tumor microenvironment (Siegel & Bilotti, 2009; Tariman & Faiman, 2010). Numerous cytokines are thought to play a role in the pathogenesis of MM and the secondary clinical findings common to the disease (Table 1). Interleukin-6 (IL-6), a primary cytokine implicated in the pathogenesis of MM, is thought to confer a proliferative and antiapoptotic advantage, thereby increasing treatment resistance (Tariman & Faiman, 2010). It is also implicated in the pathogenesis of myeloma bone disease and the increased risk of thrombosis (Palumbo et al., 2008). Evaluation of IL-6 and other cytokine levels is used primarily in the clinical trial or laboratory setting, as standardized testing technologies are not widely available for this purpose.

Genetics and MM

Genetic abnormalities have also been implicated in the pathogenesis of MM (Table 1). Translocations that involve the immunoglobulin heavy gene (IgH) locus on chromosome 14 may result in oncogene dysregulation and are associated with high-risk disease (Siegel & Bilotti, 2009). Other genetic

changes implicated in the pathogenesis of MM and associated with high-risk disease include deletion of chromosomal region 17p13 [del(17)] associated with inactivation of *p53*, monosomy of chromosome 13 [del(13)], and nonhyperdiploid disease, which is present in 50% of MM cases. Inclusion of these cytogenetic findings in the original diagnostic evaluation of MM is critical to personalized risk-adapted treatment selection and ongoing monitoring of response. Bone marrow samples are required for evaluation.

The majority of MM cells are fully differentiated. Therefore, mitosis is less frequent, limiting the utility of standard cytogenetic testing. Fluorescence in situ hybridization (FISH) for analysis of t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities is recommended for the initial diagnosis of MM (Fonseca et al., 2009; Kumar et al., 2010; Siegel & Bilotti, 2009). More recently, gene expression profiling has been incorporated into clinical trials. Gene expression profiling technology has been particularly useful in characterizing additional molecular attributes of MM and associated clinical phenomenon such as identification of the Wnt-signaling antagonist Dickkopf-related protein 1 (DKK1), an inhibitor of osteoblast differentiation. DKK1 is associated with the presence of lytic bone lesions in MM (Siegel & Bilotti, 2009). Cytogenetic or molecular responses are not currently incorporated into the response criteria for MM; thus, repeat cytogenetics, FISH, or gene expression profiles are not routinely measured outside of the clinical trial or bone marrow transplant setting.

Immunoglobulins

Genetic and molecular defects lead to overproduction of abnormal plasma cells and associated proteins that may be detected in the serum (immunoglobulins) or urine (Bence-Jones proteins) of MM patients. Myeloma cells produce large quantities of one abnormal immunoglobulin (monoclonal protein, or M protein). These immunoglobulins include heavy chain M proteins (IgG [52%], IgA [21%], IgD [2%], IgE [< 0.01%]), and light chain M proteins (kappa [κ] or lambda [λ]; Kyle et al., 2006). Overproduction of the heavy chain M protein IgM (12%) is rare in MM and is typically associated with Waldenström's macroglobulinemia.

These abnormal plasma cells have the ability to infiltrate the bone marrow and bone, producing secondary effects of lytic lesions, hypercalcemia, and cytopenias (Jagannath, Kyle, Palumbo, Siegel, Cunningham, & Berenson, 2010). In addition, increased levels of circulating myeloma proteins may lead to renal impairment, neurologic disease, and immunodeficiency. Measurements of these monoclonal proteins and evaluation of their secondary effects provide the basis for the initial diagnosis of MM.

Initial Diagnostic Evaluation of MM

The initial diagnostic evaluation of MM includes both laboratory and radiologic studies to confirm the diagnosis of MM, determine the subtype and stage, estimate prognosis, and identify the need for immediate intervention (Kurtin, 2010; NCCN, 2010; Figure 1). The diagnosis of MM is based on the level of M protein in the serum or urine, the percentage of plasma cells present in the bone marrow, and the presence or absence of end-organ damage commonly described as the CRAB criteria (Kuehl & Bergsagel, 2002; Durie et al., 2003; Figure 2). Evaluation of MM-related end-organ dysfunction (hypercalcemia, cytopenias, renal impairment, and bone disease) is necessary to determine whether the patient has symptomatic MM and requires active treatment.

Patients who are found to have active MM are then staged according to two primary staging systems—the Durie-Salmon staging system and the International Staging System (ISS) for Myeloma (Durie & Salmon, 1975; Greipp et al., 2005; Table 2). The Durie-Salmon system provides a measure of tumor burden using the number of myeloma-related bone lesions seen on x-ray and concentrations of serum calcium, serum monoclonal protein, and urine Bence-Jones protein to classify patients as having stage I, II, or III disease (Durie & Salmon, 1975). The ISS criteria were developed to incorporate diagnostic tests that provide valid prognostic data, are widely available and reasonably priced, and are therefore easily reproducible in a variety of clinical settings.

Beta$_2$-microglobulin and Serum Albumin

The beta$_2$-microglobulin (β_2M) level has been recognized as the single most reliable

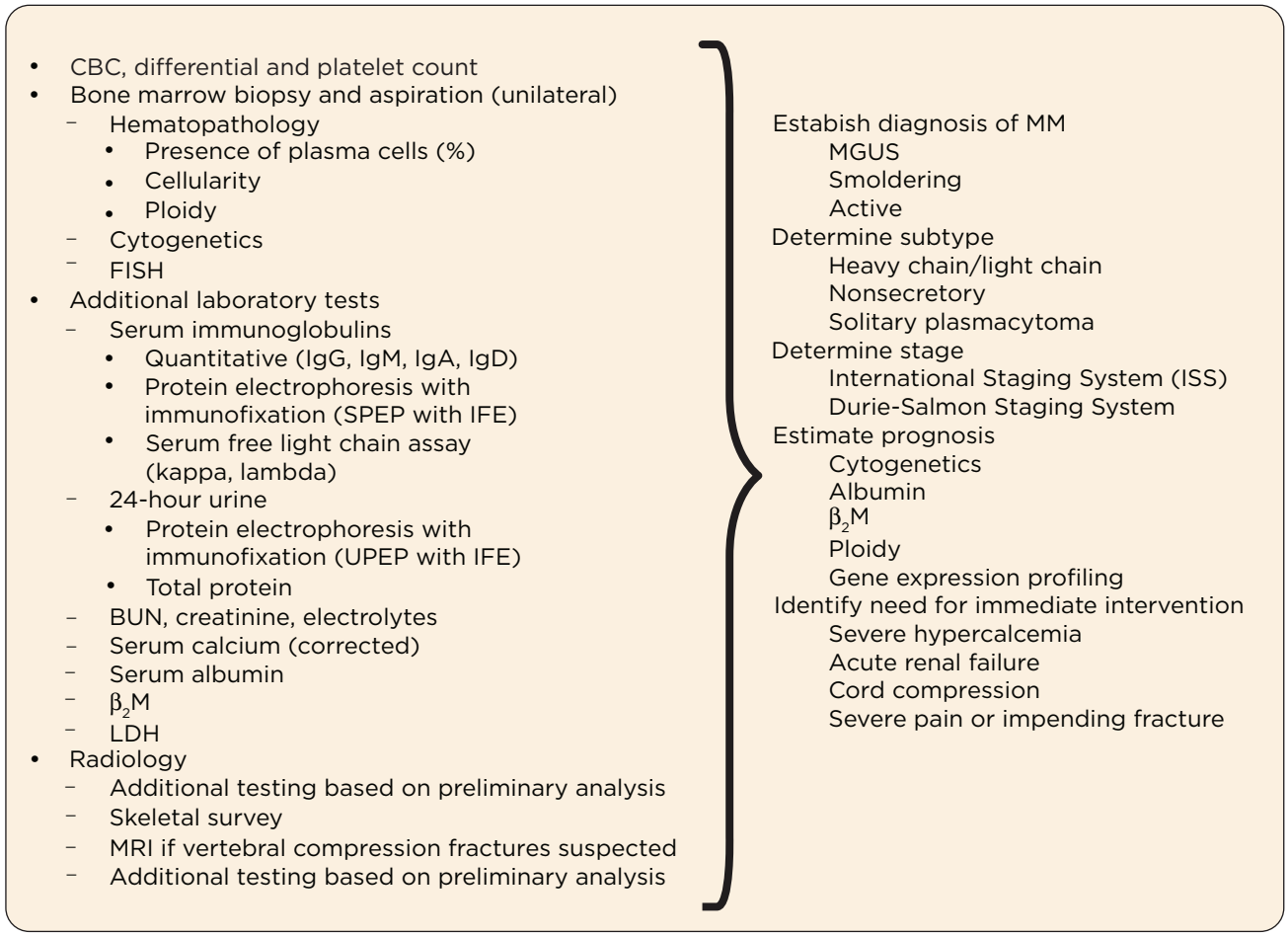

Figure 1. Initial diagnostic evaluation of suspected multiple myeloma (NCCN, 2010). β_2M = beta$_2$-microglobulin; BUN = blood urea nitrogen; CBC = complete blood cell count; FISH = fluorescence in situ hybridization; Ig = immunoglobulin; LDH = lactate dehydrogenase; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging. Courtesy of S. Kurtin and Meniscus Educational Institute, 2010

predictor of survival duration since the early 1980s (Durie, Stock-Novack, & Salmon, 1990). This was validated in the ISS analysis with clinical and laboratory data of 10,750 patients analyzed from 17 international sites, finding that a combination of serum β_2M and serum albumin provided a simple, clinically useful, and valid measure of prognosis (Greipp et al., 2005). The ISS provides a measure of proliferative tumor and prognostic information based on multivariate analysis of clinical features—specifically, β_2M and serum albumin. Patients are categorized as stage I (median survival, 62 months), stage II (median survival, 44 months), or stage III (median survival, 29 months; Greipp et al., 2005).

It is important to note that the serum albumin level < 3.5 mg/L provided consistent prognostic value vs. the β_2M alone and upstaged 1,020 patients from stage I to stage II disease, confirming the prognostic value of the combination of the two tests. The exact role of a low serum albumin level is not understood but may reflect effects on the liver by IL-6 produced by the microenvironment of myeloma cells (Durie et al., 2003). Other attributes shown to have prognostic value in this analysis included advanced age (> 65 years), hemoglobin level < 10 g/dL, platelet level < 130,000/L, high bone marrow infiltration, and poor performance status.

Serum Free Light Chains

Although the presence of an M protein is detectable in the urine or serum in 97% of patients with MM, 1% to 2% of patients have

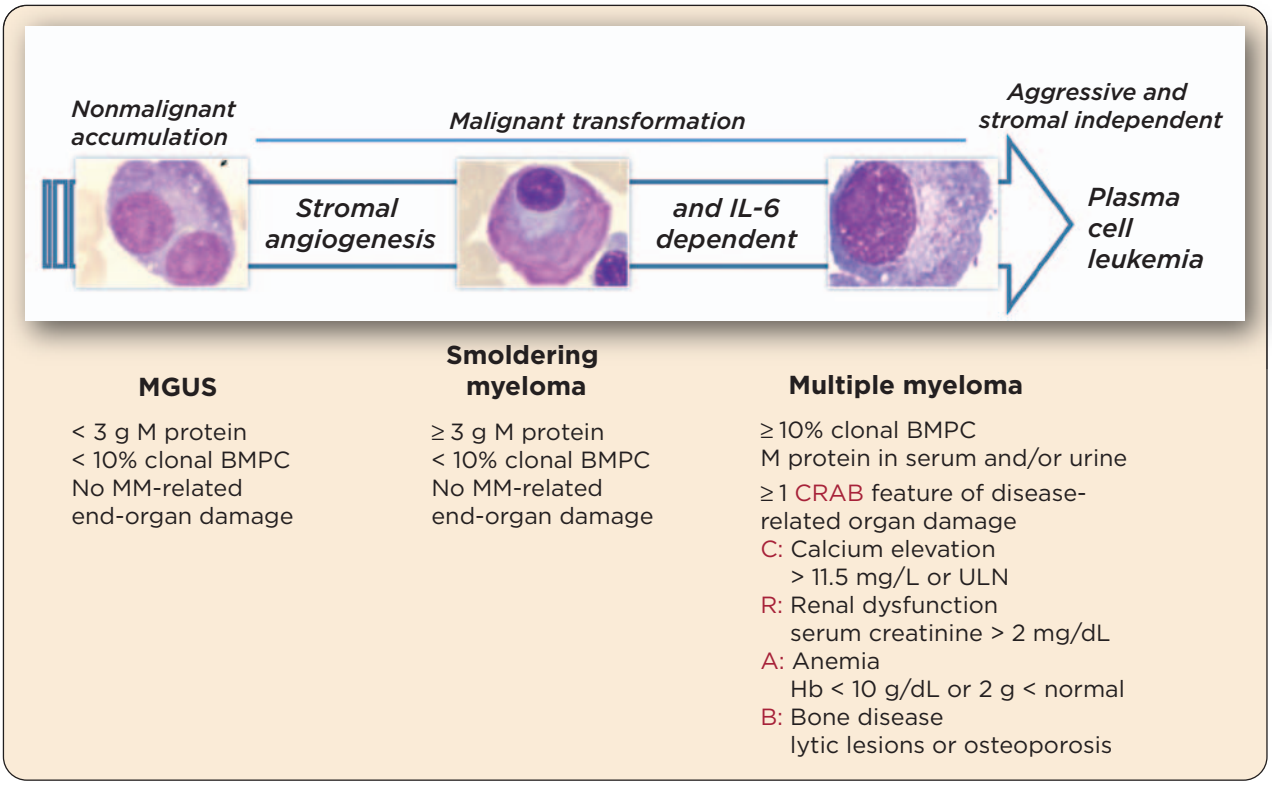

Figure 2. Multiple myeloma disease trajectory and diagnostic criteria. Data from Durie et al., 2003; Kuehl & Bergsagel, 2002; Siegel & Bilotti, 2009; Vacca & Ribatti, 2006. BMPC = bone marrow plasma cells; Hb = hemoglobin; IL-6 = interleukin-6; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; M protein = monoclonal protein; ULN = upper limit of normal. Courtesy of S. Kurtin and Meniscus Educational Institute, 2010.

nonsecretory myeloma, oligosecretory MM, or light chain amyloidosis with no M protein detectable on serum or urine electrophoresis and immunofixation (Kyle & Kumar, 2009). The development of the serum free light chain (SFLC) assay, which measures levels of free κ and λ immunoglobulin, in combination with serum protein electrophoresis (SPEP) plus immunofixation electrophoresis (IFE) or urine protein electrophoresis (UPEP) with IFE, has been found to have high sensitivity in the diagnosis of MM and may replace the 24-hour urine assay for most related diagnoses, with the exception of amyloidosis (Dispenzieri et al., 2009). In addition, the SFLC assay provides prognostic value in almost all plasma cell disorders. Evaluation of 653 patients with previously untreated MM from 36 Eastern Cooperative Oncology Group (ECOG) institutions found that elevated SFLC levels were associated with the presence of IgH translocations, known to be associated with high-risk genetic abnormalities (Kumar et al., 2010).

Serum concentrations of free light chains (FLC) are dependent on the balance between production by plasma cells and clearance through the renal glomeruli, with a serum half-life of 2 to 4 hours. Elevated κ and λ FLC may result from a variety of other clinical diagnoses including immunosuppression or stimulation, reduced renal clearance, or monoclonal plasma cell proliferative disorders. The k/λ FLC ratio (rFLC), however, usually remains normal in these conditions, and a significantly abnormal k/λ rFLC is most often due to a B lymphocyte proliferative disorder. Use of the rFLC during treatment is limited by the fact that treatment-related immunosuppression causes a marked drop in the uninvolved FLC (κ or λ), which produces an exaggerated rFLC, reflecting the degree of immunosuppression more than the tumor burden. Therefore, it is imperative to consider the measures of rFLC in the context of the treatment trajectory and overall clinical situation.

Table 2. Multiple myeloma staging systems

Stage	Durie-Salmon Staging System (1975)	International Staging System (2005)
I	Hemoglobin > 10 g/dL Calcium normal or ≤ 12 mg/dL Normal skeletal survey or solitary plasmacytoma Low M-protein production • IgG < 5 g/dL • IgA < 3 g/dL Bence-Jones protein < 4 g/24 h	β_2M ≤ 3.5 g/dL and albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One of the following • Hemoglobin < 8.5 g/dL • Calcium > 12 mg/dL • Multiple lytic bone lesions • High M-protein component - IgG > 7 g/dL - IgA > 5 g/dL - Bence-Jones protein > 12 g/24 h	β_2M ≥ 5.5 g/dL

Note: β_2M = beta$_2$-microglobulin; Ig = immunoglobulin.
Data from Durie & Salmon, 1975; Greipp et al., 2005.

Given the diagnostic and prognostic value of SFLC measures, the rFLC has been added to the International Myeloma Working Group (IMWG) response criteria. The IMWG recently published the updated response criteria, which incorporate the FLC assay (Table 3).

Evaluation of Treatment Response

In 2006, the IMWG developed a set of uniform criteria to evaluate response of MM to treatment. The European Group for Blood and Marrow Transplant (EBMT) group also has established response criteria, which have been used in the majority of historic clinical trials (NCCN, 2010; Table 3). It is important to recognize which criteria are being used in evaluating the response to therapy and the implications of selected response criteria for individual patients during their treatment.

One of the primary treatment decisions at the time of diagnosis is eligibility for high-dose therapy (HDT) followed by autologous stem cell transplant (auto-SCT). Another way to view this decision is the goal of "cure" vs. control (Rajkumar, 2008; Palumbo & Rajkumar, 2009). Prior to the use of auto-SCT and the introduction of novel agents such as bortezomib, lenalidomide, and thalidomide, which target many of the genetic and molecular abnormalities in MM, achievement of a complete response was uncommon (Durie, 2010). Obtaining a complete response is considered a surrogate marker for overall survival but is rarely achieved without aggressive up-front treatment. Several studies suggest the benefit of achieving a durable complete response is most important in patients with adverse prognostic indicators and more aggressive disease (Durie, 2010; Harousseau, Attal, & Avet-Loiseau, 2009).

It is important to remember that despite achievement of a complete response, MM remains an incurable disease. Thus, in patients not eligible for auto-SCT, the primary goals of therapy are to obtain a durable response while preserving quality of life and minimizing treatment-related adverse events. Complete disease evaluation and determination of the goals of treatment at the time of diagnosis are critical to treatment selection, preservation of stem cell collection in transplant-eligible patients, and avoidance of unnecessary toxicity in patients for whom control of the disease is the primary goal. Recent data suggest that treatment with selected agents should be continued until disease progression or unacceptable toxicity, as the depth of response may improve with continued treatment (Harousseau et al., 2009; Durie, 2010). Knowledge of strategies for evaluation of response will promote optimal therapy by reducing the potential for continuing ineffective therapy or prematurely discontinuing effective therapy.

Individual Measures of Disease Evaluation

Ongoing evaluation of treatment response using the IMWG or EBMT criteria will require evaluation of selected laboratory measures at baseline and at regular intervals (Table 4). The current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myeloma (NCCN, 2010) suggest monitoring quantitative immunoglobulins, quantitation of

Table 3. European Bone Marrow Transplant (EBMT) and International Myeloma Working Group (IMWG) response criteria

Category	EBMT criteria	IMWG criteria
Complete response (CR)	No M protein detected in the serum or urine by IFE for ≥ 6 wk ≤ 5% BMPC	Negative serum and urine IFE Resolution of plasmacytomas ≤ 5% BMPC
Stringent CR (sCR)	Not used	CR *plus* Normal FLC ratio No evidence of clonal BMPC by IHC or FISH
Very good partial response (VGPR)	Not used	Serum and urine M protein detectable by IFE but not by SPEP *or* ≥ 90% reduction in serum M protein plus urine M protein < 100 mg/24 h
Partial response (PR)	> 50% reduction in serum M protein and/or 90% reduction in urine FLC excretion or reduction to < 200 mg/24 h for 6 wk	50% reduction in serum M protein and reduction in 24-hour urine protein by ≥ 90% or to < 200 mg/24 h If immeasurable M protein: • ≥ 50% reduction in difference between involved and uninvolved FLC • ≥ 50% reduction in the size of plasmacytoma is present at baseline

Note: BMPC = bone marrow plasma cells; FISH = fluorescence in situ hybridization; FLC = free light chain; IFE = immunofixation electrophoresis; IHC = immunohistochemistry ; SPEP = serum protein electrophoresis. Data from Durie et al., 2006; Kyle et al., 2006; Harousseau, Attal, & Avet-Loiseau, 2009.

M protein (in both urine and serum), complete blood count, differential and platelet counts, blood urea nitrogen, creatinine, and serum calcium levels every 3 to 6 months for all patients (category 1 level of evidence; NCCN, 2010). Additional evaluation using repeat bone marrow biopsy and aspirate, SFLC analysis, and selected radiology testing should be repeated as clinically indicated. Radiologic testing includes a complete skeletal survey and, in selected cases, a CT scan or PET/CT. The frequency and utility of each test must be evaluated within the context of treatment goals and the individual patient as well as cost efficiency. It is also important to note that parameters for each test may vary between diagnostic facilities; consistent use of a single laboratory or imaging center will produce the most reliable values for comparison.

Implications for Advanced Practice

Multiple myeloma is a heterogenous plasma cell malignancy with variable clinical presentation, pathologic characteristics, prognosis, and recommended treatment. There is no single biomarker for the diagnosis and ongoing monitoring of MM. To date, MM is considered incurable but highly treatable, although many clinicians approach therapeutic strategies with the intent to treat for cure vs. control of the disease. The key to effective clinical management is a personalized approach to risk-adapted treatment selection based on current scientific knowledge of particular diagnostic and prognostic attributes.

Advanced practice clinicians play a critical role in this process, as they are frequently involved in the process of diagnosis, performing bone marrow biopsies, ordering and interpreting laboratory testing, and evaluating treatment response. Given the incurable nature of this disease, providing the best therapeutic option for each patient while preserving quality of life and independent function should remain a priority. Obtaining all of the data necessary for an accurate diagnosis and risk analysis is essential to selecting the best treatment for each patient.

Early identification of transplant eligibility and consideration of patient- and disease-related factors, together with the expectations of the patient, are necessary for long-term treatment planning. Ongoing evaluation of

Table 4. Laboratory measures for the diagnosis, clinical management, and evaluation of treatment response in multiple myeloma

Laboratory measure	Clinical application	Clinical considerations	Recommended frequency
Unilateral bone marrow aspirate and biopsy			
Aspirate			
IHC and flow cytometry	Detection of monoclonal plasma cells	Plasma cell infiltration may be underestimated (hemodilute or heterogeneous involvement) Requires invasive and potentially painful procedure	At diagnosis, then as clinically indicated
FISH	Identification of molecular markers	More sensitive than conventional cytogenetics Expensive	At diagnosis for risk-stratification
Cytogenetics	Identification of karyotype	Abnormalities undetectable by conventional cytogenetics in ~30% of MM cases due to lack of metaphases Less expensive than FISH Useful in excluding other disease states at diagnosis Cytogenetics have prognostic value	At diagnosis for risk-stratification and then as clinically indicated
Ploidy	Determined by cytogenetic profile	Nonhyperdiploid MM (40%–50% of MM) is associated with translocation involving the IgH on chromosome 14 and is associated with activation of various oncogenes and a more aggressive subtype Hyperdiploid MM is associated with trisomies of odd-numbered chromosomes (3, 5, 7, 9, 11, 15, 19, 21) and is observed in 50%–60% of patients with MM	At diagnosis for risk stratification
Trephine biopsy	Determination of cellularity, identification of sheets of plasma cells Helpful if aspirate is hemodilute or not obtained	Requires an invasive and potentially painful procedure	At diagnosis, then as clinically indicated
Peripheral blood			
Serum quantitative immunoglobulins	Identification and quantitation of M protein: IgG (60%); IgA, IgD, IgE, IgM (Waldenström's macroglobulinemia)	Variable measures in individual labs Most commonly used measure to diagnose and evaluate MM Relatively inexpensive Easy to obtain	At diagnosis, then every 3–6 mo or as clinically indicated (category 1); more frequent monitoring with initiation of a new therapy
Serum protein electrophoresis (SPEP)	Identification of M-spike	Necessary for categorization of disease and staging based on Durie-Salmon criteria	At diagnosis, then as clinically indicated
Serum immunofixation electrophoresis (SIFE)	Identification of heavy or light chain type	Not quantitative More expensive than electrophoresis Lowest detectable level of M component: 0.12–0.25 g/dL	At diagnosis, then as clinically indicated
CBC, differential, and platelet count	Evaluation of bone marrow function and presence of cytopenias	Necessary for categorization and staging of disease Critical to aggressive management of disease or treatment-related cytopenias	At diagnosis, then determined by treatment; may be as often as weekly to biweekly with initiation of therapy or in the presence of cytopenias
β_2M	Measure of tumor burden	Necessary for staging of disease using ISS criteria Level is affected by renal clearance; may be falsely elevated in renal insufficiency or failure	At diagnosis, then every 3–6 mo or as clinically indicated
Calcium/albumin	Indication of end-organ damage	Necessary for diagnosis of active MM and staging using ISS criteria Corrected calcium should be calculated for accurate reflection of disease state	At diagnosis, then frequency determined by baseline measures, treatment, and clinical status
BUN/creatinine	Indication of end-organ damage	Necessary for diagnosis of active MM and staging using Durie-Salmon criteria May identify patients needing immediate interventions for renal failure	At diagnosis, then frequency determined by baseline measures, treatment, and clinical status

Table 4 (cont'd). Laboratory measures for the diagnosis, clinical management, and evaluation of treatment response in multiple myeloma

Laboratory measure	Clinical application	Clinical considerations	Recommended frequency
Serum electrolytes	Baseline evaluation of electrolyte abnormalities	Electrolyte abnormalities (hypokalemia, hypomagnesemia) may be present at diagnosis	At diagnosis, then frequency determined by baseline measures, treatment, and clinical status
LDH	Measure of tumor burden	Elevated LDH level has been associated with inferior clinical outcomes Measures vary in individual laboratories Levels may be falsely elevated with administration of granulocyte-stimulating proteins	At diagnosis, then frequency determined by baseline measures, treatment, and clinical status
Uric acid	Baseline assessment for risk of tumor lysis in aggressive subtypes of MM		As clinically indicated
Serum free light chain assay (FLC)	Determination of involved free light chain (iFLC), either kappa (κ) or lambda (λ)	Necessary for response assessment in non-secretory MM Sufficient to screen for plasmaproliferative disorders in combination with SPEP and IFE. If a diagnosis of PCD is made, 24-h urine for UPEP and IFE is required for all patients to complete staging. Expensive Necessary for defining sCR Not useful in evaluation of PR or CR Differences in recommendations for EBMT vs. IMWG criteria for response	At diagnosis for nonsecretory MM, then every 3–6 mo or for determination of sCR; may be monitored more frequently in the setting of clinical trials
Serum viscosity	Indicated for IgM subtype and high serum protein levels (> 7 g/dL)	Identification of patients who may benefit from plasmapheresis Most common in Waldenström's macroglobulinemia	At diagnosis, then as clinically indicated; repeat for ongoing evaluation if abnormal
Plasma cell labeling index (PCLI)	Primarily in clinical trials	Provides prognostic information	Primarily in clinical trials
24-hour urine			
Total protein	General measure of urinary protein load		At diagnosis, then as clinically indicated
Albuminuria	Measure of early renal insufficiency		At diagnosis, then as clinically indicated for patients testing positive
Urine protein electrophoresis (UPEP) Urine immunofixation electrophoresis (UIFE)	Detection of Bence-Jones protein (M protein) in the urine Identification of light chain/heavy chain subtypes	Combination of UPEP and IFE is necessary for completion of diagnosis and staging for all patients with positive screening for plasmaproliferative disorders Use of FLC analysis as a surrogate for UPEP with IFE in response assessment is not recommended for patients with positive urinary M proteins at diagnosis Inexpensive Sometimes difficult to complete accurately	If a diagnosis of PCD is made, 24-h urine for UPEP and IFE is required for all patients to complete staging Should be repeated every 3–6 mo or as clinically indicated if positive at baseline

Note: β_2M = beta$_2$-microglobulin; BUN = blood urea nitrogen; CBC = complete blood cell count; CR = complete response; EBMT = European Group for Bone and Marrow Transplant; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; ISS = International Staging System for Myeloma; IMWG = International Myeloma Working Group; LDH = lactate dehydrogenase; M protein = monoclonal protein; MM = multiple myeloma; PCD = plasma cell dyscrasia; PR = partial response; sCR = stringent complete response. Data from Anderson et al., 2009; Dispenzieri et al., 2009; Fonseca et al., 2009; Harousseau, Attal, & Avet-Loiseau, 2009; Kumar et al., 2009; Kurtin, 2010; NCCN, 2010.

response requires a working knowledge of the pathobiology of MM, clinical findings including biomarkers, current criteria for evaluation of response, and secondary options for treatment. The consistent application of diagnostic and response criteria including key laboratory measures is crucial to promoting the selection and continuation of effective therapies.

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