Updates in the Diagnosis and Monitoring of Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a plasma cell neoplasm characterized by malignant transformation and clonal expansion of mature plasma cells, resulting in an overproduction of monoclonal proteins (immunoglobulins). Due to the heterogeneity of the disease, there is wide variability in the disease trajectory and prognosis. To date, MM is considered an incurable disease, and nearly all patients will relapse and require successive lines of therapy to survive. Each relapse is characterized by a lower depth and shorter duration of response. In the absence of a definitive cure, the goal of therapy has been to improve progression-free survival and, in turn, overall survival. However, as patients survive longer and receive continued lines of therapy, it is important to preserve quality of life in these individuals for whom long-term control of disease is the main goal. As such, accurate diagnosis and risk stratification is critical to selecting the best therapy at the time of diagnosis. Early identification of relapse or lack of response to therapy will facilitate changes in therapy to maximize disease control. Early detection of progressive disease and monitoring of adverse events are essential to provide the best therapy over the course of the patient's disease. The International Myeloma Working Group (IMWG) has recently updated recommendations for the diagnosis and monitoring of MM. Familiarity with the updated IMWG recommendations will provide the advanced practitioner in oncology with the tools for the effective diagnosis, treatment, and monitoring of the MM patient.

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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 monoclonal proteins (immunoglobulins). The pathophysiology of the disease is a result of complex interactions between the bone marrow microenvironment and the malignant clone. These processes result in the characteristic

findings of end-organ damage involving the kidneys and bones, and associated clinical findings including azotemia or acute kidney injury, anemia, hypercalcemia, pain, fatigue, fractures, hyperviscosity, and neuropathy. Multiple myeloma remains an incurable but highly treatable disease; however, multiple relapses and eventual death are inevitable for the majority of patients. Fortunately, the pace at which new therapies, improved diagnostics, and improved supportive care strategies have been developed or refined for patients with MM is unprecedented. 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. Identifying criteria for progression and relapsed or refractory disease is essential to individualizing treatment and supportive care for the MM patient. This paper summarizes these changes by updating a previous publication in this journal (Kurtin, 2010), with integration of current recommendations for the diagnosis, risk stratification, and monitoring of response in MM. A case study will be used to illustrate the diagnosis and monitoring of a patient with MM.

DISEASE OVERVIEW

Multiple myeloma is clinically and pathologically heterogeneous, resulting in wide variability in response to treatment and survival. As a result of advances in laboratory techniques and genetic analyses, patients newly diagnosed with MM can be categorized into different risk groups (Table 1). This stratification assists in identifying those patients who are candidates for standard therapies including novel agents, autologous stem cell transplantation, and clinical trials. Importantly, when used in combination with established therapies, novel agents such as bortezomib (Velcade), carfilzomib (Kyprolis), lenalidomide (Revlimid), pomalidomide (Pomalyst), and thalidomide (Thalomid) have neutralized some high-risk features, contributing to improved treatment outcomes (Mikael, 2014). More recently, panobinostat (Farydak), ixazomib (Ninlaro), daratumumab (Daralex), and elotuzumab (Empliciti) were approved, offering expanded options for treatment. The refinement of supportive care measures and techniques for autologous peripheral stem cell transplant has also improved survival in MM (NCCN, 2016). All new agents evolve from clinical trials, so consideration of clinical trial enrollment is encouraged from the time of diagnosis and throughout the course of the disease. All patients with MM should receive concurrent palliative and supportive care, as discussed elsewhere in this supplement (Richards & Brigle, 2015).

BONE MARROW FEATURES AND ASSOCIATED MM PATHOBIOLOGY

Multiple myeloma is a clonal plasma cell malignancy that results from a complex interaction between 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. Multiple myeloma cells adhere to the extracellular matrix and bone marrow stromal cells, resulting in a cascade of events including release of cytokines from both the bone marrow stroma and MM cells. This interaction leads to the proliferation and survival of MM cells, autocrine production of additional cytokines, and in some patients, drug resistance (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). Numerous cytokines are thought to play a role in both the pathogenesis of MM and secondary clinical findings common to the disease. Interleukin-6 (IL-6), a primary cytokine implicated in the pathogenesis of MM, is associated with more aggressive disease and resistance to novel agents (Hunsucker et al., 2011; Voorhees et al., 2007), and is thought to confer a proliferative and antiapoptotic advantage to the malignant cell (Anderson et al., 1989; Kawano et al., 1988). IL-6 is also thought to increase the risk of thrombosis (Palumbo et al., 2008) and has been implicated in the pathogenesis of myeloma bone disease as a stimulator of osteoclastogenesis (Duplomb et al., 2008). Noncardiac C-reactive protein levels are commonly used as a surrogate marker for IL-6 (Orlowski et al., 2015). Measures of other cytokine levels are used primarily in clini-

cal trials or in the laboratory setting as standardized testing technologies are not yet widely available for routine testing.

GENETICS AND MM

Genetic instability is implicated in the pathogenesis of MM, and bone marrow samples are required for evaluation. Translocations involving the immunoglobulin heavy gene (IgH) locus on chromosome 14 to one of several oncogenes are the most common genetic changes. These may result in oncogene dysregulation and clonal evolution that is associated with high-risk disease (Bianchi & Anderson, 2014; Mikael et al., 2014). Other genetic changes conferring high-risk disease include the deletion of chromosomal region 17p13, which is associated with the inactivation of p53, monosomy of chromosome 13 [del(13)], and nonhyperdiploidy. Inclusion of these cytogenetic findings in the original diagnostic evaluation of MM is critical to personalized risk-adapted treatment selection.

Plasma cells represent the end-product of the B-cell differentiation pathway. Therefore, the majority of MM cells are fully differentiated with less frequent mitosis, limiting the utility of standard cytogenetic testing. As a result, the concurrent use of 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), deletion of chromosome 13, presence of chromosome 1 abnormalities, and identification of ploidy category is recommended for the initial diagnosis of MM (Rajkumar et al., 2014). More recently, gene expression profiling has been incorporated into clinical trials, providing additional prognostic information. Emerging evidence suggests that, over the course of the disease, clonal competition and clonal evolution result in the survival and emergence of a dominant clone with increasingly aggressive features. As a result, full diagnostic evaluation is recommended at each episode of progression (Keats et al., 2012). With the advent of gene expression profiling, the concept of minimal residual disease (MRD) as a surrogate marker for molecular remission has been suggested as the best indicator for improved long-term disease-free survival (http://bsri.myeloma.org). Common genetic and molecular abnormalities associated with MM are provided in Table 1.

IMMUNOGLOBULINS

Genetic and molecular defects lead to the proliferation of abnormal plasma cells and their associated proteins that may be detected in the serum (immunoglobulins) or urine (Bence-Jones protein) of patients with MM. Myeloma cells produce large quantities of a single abnormal immunoglobulin (monoclonal protein, or M-protein). These immunoglobulins are comprised of a heavy-chain M-protein (IgG [52%], IgA [21%], IgD [2%], IgE [< 0.01%]) and light-chain M-protein (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 both the bone marrow and cortical bone, producing secondary effects of cytopenias, lytic lesions, and hypercalcemia (Jagannath, Kyle, Palumbo, Siegel, Cunningham, & Berenson, 2010). In addition, increased levels of circulating myeloma proteins may lead to renal impairment, neurologic disease, and immunodeficiency.

Measurement of these monoclonal proteins and evaluation of their secondary effects provide the basis for the initial diagnosis of MM. Serum protein electrophoresis (SPEP) with immunofixation (IFE) is a qualitative test that, together with quantitative immunoglobulin assays, have been the standard for identification and measurement of monoclonal proteins. Importantly, monoclonal IgA proteins are unique in that they can migrate into the β region on an SPEP; thus, SPEP with immunofixation may provide inaccurate quantification of the IgA monoclonal protein (Boyle et al., 2015; Katzmann et al., 2015). As a result, assays that utilize immune precipitation total IgA are recommended for patients having IgA MM. Note, however, that this assay may also lead to inaccurate quantification as it does not distinguish between monoclonal and polyclonal IgA (Boyle et al., 2014).

More recently, the IgA Hevylite (HLC) test, which measures IgA κ and IgA λ separately and provides precise quantitative measurements of monoclonal IgA expression and polyclonal isotype-matched suppression, has been evaluated to overcome these limitations (Binding Site, 2015; Boyle et al., 2014). HLC assays can be used to

Table 1. Risk Stratification of Multiple Myeloma

Risk categories, with incidence and survival	Attributes		
	FISH	GEP	Other features
High incidence: 20% Median OS: 3 yr	Del(17p) t(14;16) t(14;20) 1q21 Del(1q)	High-risk signature Cyclin D1 t(11;14) C-maf t(14;16); Cyclin D3 t(6;14); mafB t(14;29); p53 dysregulation (17p13)	At diagnosis: Elevated LDH β_2M > 4 mg/L Serum albumin < 3 g/dL Nonhyperdiploid ISS stage III Bone marrow plasma cells > 50% Frail Complex or poorly controlled comorbidities At relapse/progression: Primary refractory disease Relapse < 12 months from HSCT or first-line therapy Aggressiveness of relapse/plasma cell leukemia Poor bone marrow reserve Renal failure Unresolved toxicity (e.g., neuropathy)
Intermediate incidence: 20% Median OS: 4–5 yr	t(4;14) del 13	*MMSET* gene	Hypoploidy Plasma cell labeling index ≥ 3% Intermediate fitness
Standard incidence: 60% Median OS: 8–10 yr	t(11;14) t(6;14)		Fit No or well-controlled comorbidities Hyperploidy

Note. OS = overall survival; FISH = fluorescence in situ hybridization; GEP = gene expression phenotype; LDH = lactate dehydrogenase; β_2M = beta2-microglobulin; ISS = International Staging System; HSCT = hematopoietic stem cell transplant; MMSET = multiple myeloma SET domain. Adapted from Kurtin (2010). Data from Rajkumar et al. (2014); Mikhael (2014); Palumbo et al. (2015); Bianchi & Anderson (2014); Mikhael et al. (2013); Fonseca & Monge (2013).

monitor IgA MM and provide information similar to the combination of SPEP, IFE, and IgA quantification (Boyle et al., 2014, Katzmann et al., 2015; Binding Site, 2015). In an evaluation of sera from 157 patients with IgA MM (100 with IgA κ, 57 with IgA λ), all samples were found to have abnormal IgA heavy:light chain (HLC) ratios, and the SPEP bands were quantifiable in only 105 of 157 samples (67%) (median, 28.5 g/L [range, 2.2–98 g/L]) (Boyle et al., 2015). Elevated IgA HLC ratios have been associated with inferior overall survival (Boyle et al., 2014; Ludwig et al., 2013).

In a similar study, Ludwig and colleagues (2013) noted that patients with HLC ratios remaining abnormal after achieving a partial response (PR) or better had a significantly shortened survival as compared with those achieving a normal HLC ratio (40.5 months, 95% CI = 17–65 vs median not reached; hazard ratio [HR] 2.8, 95% CI = 0.99–8.3; $p < .03$). Additionally, in univariate Cox analysis, an increasingly abnormal HLC ratio (< 0.022 or > 45) and a β2-microglobulin concentration of 45.5 mg/L at presentation were associated with shorter survival (HR 1.88, 95% CI = 1.1–3.1; $p = .015$, and HR 2.2, 95% CI = 1.3–3.9; $p = .016$, respectively). In contrast, no correlation was found for the other parameters tested (FLC ratio, albumin 435 g/L, lactate dehydrogenase 4248 U/L) (Ludwig et al., 2013).

Although changes in HLC concentration have not yet been incorporated into the International Myeloma Working Group (IMWG) criteria for diagnosis and response evaluation, additional analyses are underway to further validate the role of a commercially available Hevylite test.

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 nonsecretory myeloma, oligo secretory 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 SPEP plus IFE or urine protein electrophoresis (UPEP) with IFE, has been found to have high sensitivity in the diagnosis of MM (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). Additionally, elevated FLC levels are associated with renal complications (Heher et al., 2010).

Serum concentrations of free light chains, which are dependent on the balance between production by plasma cells and clearance through the renal glomeruli, have a serum half-life of 2 to 4 hours. Elevated κ and λ FLC may result from 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 other 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. Given the diagnostic and prognostic value of SFLC measurements, rFLC has been added to the IMWG response criteria and is included in the updated IMWG criteria for diagnosis of MM.

CASE STUDY

Following a weekend of babysitting his three young grandchildren, a 66-year-old white male presented several days later to his primary care provider (PCP) with fatigue as well as hip and back pain. Imaging studies revealed the presence of lytic lesions in the pelvis and left posterior ribs. Laboratory work drawn at that visit was notable for anemia (hemoglobin 10.9 g/dL), elevated total serum protein (11.1 g/dL), and serum calcium (10.8 mg/dL) near the upper limits of normal. The patient was referred to a local oncologist, who proceeded with the standard work-up for suspected MM.

INITIAL DIAGNOSTIC EVALUATION OF MM

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, 2016) (Figure 1). The diagnosis of MM is based on the level of M-protein in the serum or urine, percentage of plasma cells present in the bone marrow, and presence or absence of end-organ damage commonly described as the CRAB criteria (calcium elevation, renal insufficiency, anemia, or bone lesions; Durie et al., 2003; Kuehl & Bergsagel, 2002; Table 2). Evaluation of MM-related end-organ dysfunction is necessary to determine whether the patient has symptomatic MM and requires active treatment.

The IMWG has recently updated the diagnostic criteria for symptomatic MM with a shift to myeloma-defining events (MDE; Rajkumar et al., 2014). These events include evidence of myeloma-related end-organ damage or presence of any one of the newly described MDE biomarkers. End-organ damage is reflected in the classic CRAB features, whereas MDEs now include ≥ 60% clonal bone marrow plasma cells (BMPC), serum involved/uninvolved free light chain ratio of 100 or greater, or the presence of more than one focal lesion > 5 mm on MRI (Rajkumar et al., 2014). These new criteria are included based on evidence indicating patients with these disease features are at higher risk for progression to symptomatic MM; therefore, earlier treatment may prevent or reduce the severity of end-organ damage (Rajkumar et al., 2014).

The Durie-Salmon staging system and the International Staging System (ISS) are the two primary staging systems for MM (Durie & Salmon, 1975; Greipp et al., 2005; Table 3). The Durie-Salmon system provides a measure of tumor burden using the number of myeloma-related bone lesions seen on x-ray, and concen-

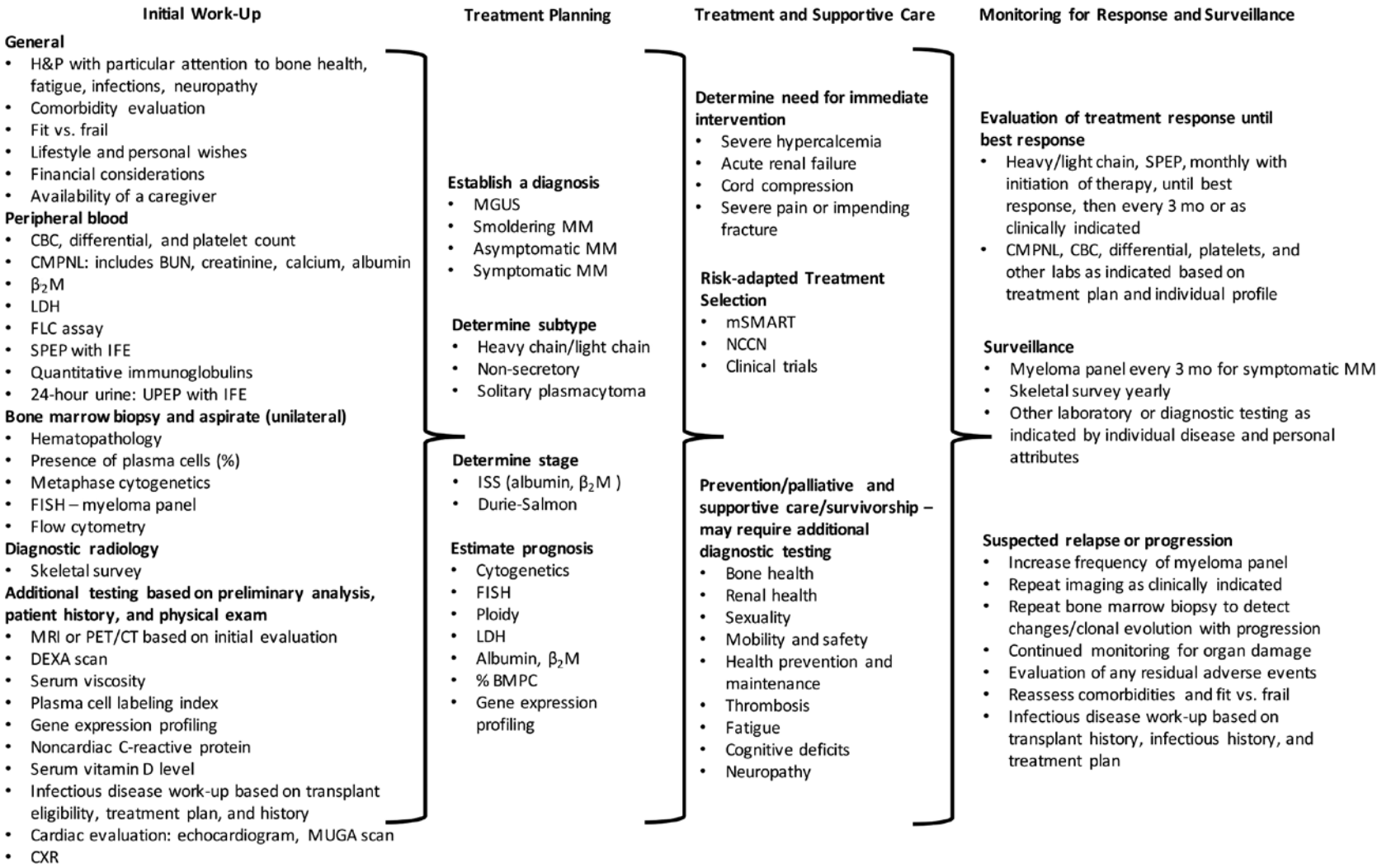

Figure 1. Diagnosis and monitoring of multiple myeloma. H&P = history and physical exam; CMPNL = comprehensive metabolic panel; β_2M = beta2-microglobulin; LDH = lactate dehydrogenase; FLC = free light chain; SPEP = serum protein electrophoresis; IFE = immunofixation; UPEP = urine protein electrophoresis; DEXA = dual energy x-ray absorptiometry; MUGA = multigated radionuclide angiography; CXR = chest x-ray; MGUS = monoclonal gammopathy of undetermined significance; FISH = fluorescence in situ hybridization; BMPC = bone marrow plasma cells; GEP = gene expression phenotype; NCCN = National Comprehensive Cancer Network; mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy. Adapted from Kurtin (2010). Data from Ludwig et al. (2014); Mikhael et al. (2013); NCCN (2015); Rajkumar et al. (2014).

trations 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 are reasonably priced, and are therefore easily reproducible in a variety of clinical settings (Greipp et al., 2005). Neither of these staging systems are sufficient alone in determining prognosis as they do not incorporate cytogenetic, molecular, or criteria for MDE that are now accepted as necessary to effectively risk stratify MM (Rajkumar et al., 2014).

CASE STUDY: CONTINUED

Results of Initial Diagnostic Evaluation:

- Peripheral blood
  - Hemoglobin 10.9 g/dL
  - Calcium 10.8 mg/dL
  - β_2-microglobulin 3.7 g/dL
  - Albumin 4.2 g/dL
  - Serum creatinine 0.9 mg/dL
  - Lactate dehydrogenase 275 units/L (upper limit of normal = 250 units/L)
- Bone marrow biopsy and aspirate
  - 72% plasma cells in sheets, with lambda light-chain restriction
  - Fluorescent in situ hybridization (FISH): t(4;14)
  - Cytogenetics: normal male karyotype: 46 XY[20]
  - Quantitative immunoglobulins, SPEP with IFE, and serum free light chains (SFL)
    - IgG monoclonal protein (3100 mg/dL)
    - Elevated lambda light chains (324 mg/L)
    - Kappa:lambda ratio (0.14)
- Imaging
  - Bone survey identified lytic lesions throughout the anterior and posterior rib cage, femurs, and in several thoracic and lumbar vertebrae
- ISS stage: II
- Durie-Salmon stage: II
- Final diagnosis: IgG lambda multiple myeloma, ISS stage II

Table 2. Diagnostic Criteria for Myeloma of Undetermined Significance, Smoldering Multiple Myeloma, and Symptomatic Myeloma

Condition	MGUS	SMM	Active myeloma
Clonal bone marrow plasma cells (BMPC)	< 10%	10–60%[a]	≥ 10% or biopsy-proven bony or extramedullary plasmacytoma AND one or more MDE (see below)
Presence of myeloma-defining events (MDE)	None	None	Yes
Monoclonal protein (M-protein)	< 30 g/L	≥ 30 g/L (IgG or IgA) serum protein; or ≥ 500 mg/24 hr urinary protein	No specific level required. Active disease is defined by MDE

Myeloma-Defining Events

Myeloma related end-organ damage (CRAB criteria, revised)

C: Calcium elevation
- Serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than ULN *OR* > 2.75 mmol/L (> 11 mg/dL)

R: Renal dysfunction
- Creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (> 2 mg/dL)

A: Anemia
- Hemoglobin > 20 g/L below LLN or < 100 g/L

B: Bone disease
- One or more osteolytic lesions on skeletal radiography, CT, or PET/CT

Any one or more biomarkers of malignancy
- BMPC > 60%
- Involved/uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesion > 5 mm on MRI studies

Note. MGUS = myeloma of undetermined significance; SMM = smoldering multiple myeloma; BMPC = bone marrow plasma cells; MDE = myeloma-defining events; ULN = upper limit of normal; LLN = lower limit of normal. Adapted from Rajkumar et al. (2014).

Based on the patient's age (66 years) and ECOG performance status of 0, he was considered to be a candidate for high-dose therapy (HDT) followed by autologous hematopoietic stem cell transplant (auto-HSCT). Given the diagnosis of ISS stage II (i.e., intermediate-risk disease), a regimen of bortezomib, lenalidomide, and low-dose

Table 3. Staging Systems Used to Estimate Myeloma Tumor Burden

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 hr	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 hr	β_2M ≥ 5.5 g/dL

Note. β_2M = beta2-microglobulin; Ig = immunoglobulin. Data from Durie & Salmon (1975); Greipp et al. (2005).

dexamethasone (VRd) was chosen as primary therapy. Monthly infusions of zoledronic acid were initiated as supportive care, and he was referred to the bone marrow transplant (BMT) center for evaluation. He achieved a very good partial response (VGPR) by the fourth cycle of therapy, at which time stem cells sufficient for two auto-HSCTs were collected. Following cycle 3 of VRD, he developed grade 2 peripheral neuropathy (PN). The bortezomib was changed to weekly subcutaneous administration to limit progressive PN (Kurtin et al., 2013). He underwent an uneventful auto-HSCT, and following recovery of his peripheral counts he was started on a maintenance regimen of lenalidomide 15 mg once daily.

EVALUATION OF TREATMENT RESPONSE

Both the IMWG and European Group for Blood and Marrow Transplant (EMBT) have established response criteria in order to standardize and uniformly analyze outcomes in the treatment of MM (Table 4). While the definitions put forth by the two groups are similar, IMWG criteria describe additional response categories and clarify a number of problematic issues inherent in the EMBT criteria. Regardless, it is important to recognize which set of criteria is being used when evaluating response for individual patients.

Ongoing evaluation of treatment response using the IMWG or EBMT criteria will require evaluation of selected laboratory measures at baseline and at regular intervals. The current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myeloma (NCCN, 2016) suggest monitoring quantitative immunoglobulins, M-protein levels (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, 2016). Additional evaluation using repeat bone marrow biopsy and aspirate, multiparameter FLC analysis, and selected radiologic testing should be repeated as clinically indicated. Radiologic testing includes a complete skeletal survey and, in selected cases, a CT, PET/CT, or MRI scan. 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.

RELAPSED DISEASE

Just as definitions have been set forth to describe response to treatment, the IMWG has also established definitions to describe myeloma that has progressed or is in relapse (Table 4). Specifically, relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy or as disease that progresses within 60 days of discontinuing the last treatment. The more general term of relapsed myeloma is defined as previously treated myeloma that now shows evidence of progression but does not fit the above definition of relapsed and refractory myeloma. In the case of relapsed disease, not all patients will require immediate therapy at first sign of relapse. Myeloma

Table 4. International Myeloma Working Group Response Criteria 2014

Response subcategory	Response criteria
Complete response	• Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26–1.65 in addition to CR criteria is required; two consecutive assessments are needed
Stringent complete response	• CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	• sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 x 10^6 total bone marrow cells analyzed by multiparametric flow cytometry (with more than four colors)
Molecular CR	• CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
Very good partial response	• Serum and urine M component detectable by immunofixation but not on electrophoresis, or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 hr; in patients for whom only measurable disease is by serum FLC level, ≥ 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
Partial response	• ≥ 50% reduction of serum M-protein and reduction in 24-hr urinary M-protein by ≥ 90% or to < 200 mg/24 hr • If serum and urine M-protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M-protein criteria • If serum and urine M-protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required • Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
Minimal response for relapsed/refractory myeloma only	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50%–89% • In addition, if present at baseline, 25%–49% reduction in size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease	• Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
Progressive disease	• Increase of ≥ 25% from lowest response value in any of following: - Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; - Urine M component (absolute increase must be ≥ 200 mg/24 hr) and/or; - Only in patients without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); - Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC level; bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) - Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder - Two consecutive assessments before new therapy are needed

Note. CR = complete response; FLC = free light chain; sCR = stringent complete response; VGPR = very good partial response; PR = partial response; M = monoclonal; MR = minimal response; SD = stable disease; PD = progressive disease. Adapted from Palumbo et al. (2015).

in relapse can be defined as being "biochemical" or "clinical" in nature. Biochemical relapse is characterized by an increase in a monoclonal protein in the absence of worsening of end-organ damage as defined by the IMWG criteria (Durie et al., 2006; Durie et al., 2007). Clinical relapse is characterized by the presence of worsening end-organ damage as defined by the CRAB criteria and is often symptomatic. Patients in clinical relapse clearly require therapeutic intervention, but the decision to treat a biochemical relapse is not so clear. Patients who experience a slow biochemical relapse may not merit the risks and side effects of initiating what may become indefinite therapy. However, patients who demonstrate signs of a rapidly progressing biochemical relapse may merit intervention even in the absence of clinical signs or symptoms. The IMWG has set forth guidelines to help determine when to begin treatment in patients with biochemical relapse. The criteria in these guidelines focus on both the absolute level and rate of increase of the monoclonal protein present in the blood or urine (Rajkumar et al., 2011).

CASE STUDY: CONTINUED

Following 21 months of lenalidomide maintenance therapy, the patient's serum monoclonal IgG level began to rise (1993 mg/dL), and a subsequent bone marrow biopsy confirmed early relapse of his disease (12% plasma cells with lambda-light chain restriction). As he had originally obtained a rapid and durable response with a regimen containing bortezomib, this agent was restarted using once-weekly subcutaneous dosing in combination with low-dose dexamethasone (Vd) He was again referred to the BMT center for consideration of a second auto-HSCT. Following cycle 2 of Vd he developed grade 2 PN. Despite a bortezomib dose reduction in the subsequent cycle of therapy, his neuropathy worsened and necessitated a treatment interruption. The neuropathic symptoms resolved over the next several months but unfortunately, during this time of dose reduction and dose interruption, his monoclonal IgG level began to rise (2235 mg/dL).

After consideration of the therapeutic goal and available treatment options, he began treatment with single-agent carfilzomib at 20 mg/m^2, which was dose escalated to 27 mg/m^2 in cycle two and for all subsequent cycles. He obtained a complete response by the fourth cycle of therapy. The patient opted to continue with carfilzomib therapy in lieu of a second auto-HSCT.

IMPLICATIONS FOR ADVANCED PRACTICE

Multiple myeloma is a heterogeneous 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 versus 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, together with patient-related factors such as comorbidities, age, and fitness.

Advanced practice clinicians play a critical role in the diagnosis and monitoring of patients with MM as they are frequently involved in the process of diagnosis, performing bone marrow biopsies, ordering and interpreting laboratory and radiological testing, and evaluating treatment response. Given the incurable nature of this disease, providing the best therapeutic options 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 patient expectations, are necessary for long-term treatment planning.

Ongoing evaluation of 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 the selection and continuation of effective therapies.

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