Multiple Myeloma: Diagnosis and Treatment

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CME Activity

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Abstract

The diagnosis and treatment of multiple myeloma has changed dramatically in the past decade. The disease definition has been updated to include highly specific biomarkers in addition to established markers of end-organ damage. The staging system has been revised to combine both measures of tumor burden and disease biology. Advances in therapy have resulted in a marked improvement in overall survival. New drugs introduced in the past few years include carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab. In this review, we outline the current approach to the diagnosis, prognosis, and management of multiple myeloma.

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Multiple myeloma (MM) is a clonal plasma cell malignant neoplasm that accounts for approximately 10% of hematologic malignant disorders.[1,2] The annual incidence, age-adjusted to the 2000 US population, is 4.3 per 100,000, resulting in over 20,000 new patients in the United States each year.[3] Multiple myeloma is twice as common in blacks compared with whites, and this racial disparity is related to the higher prevalence of monoclonal gammopathy of undetermined significance (MGUS) in blacks.[4,5] There is a slight male predominance. The median age at onset is 66 years, and only 2% of patients are younger than 40 years of age at diagnosis.[6]

Multiple myeloma evolves from a premalignant condition clinically recognized as MGUS.[7] Monoclonal gammopathy of undetermined significance is present in 3% to 4% of the general population older than 50 years.[8,9] Because MGUS is mostly asymptomatic and detected often as an incidental laboratory finding, only 10% of patients with newly diagnosed MM have a history of preexisting MGUS. However, studies have found that MGUS almost always precedes MM and is associated with a risk of

progression to MM of approximately 1% per year.[7,10] Smoldering MM (SMM) is an intermediate stage between MGUS and MM and is associated with a higher risk of progression of approximately 10% per year.[11]

Until 2000, the mainstay of therapy for MM was use of alkylators and corticosteroids[12] and in selected patients, high-dose chemotherapy with autologous stem cell transplant (ASCT).[13,14] Subsequently, thalidomide,[15] bortezomib,[16] and lenalidomide[17] emerged as effective agents and greatly improved clinical outcome.[18,19] More recently, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, and elotuzumab have been approved in the United States for the treatment of MM, substantially expanding the number of treatment regimens available for patients in all stages of the disease.

DIAGNOSIS

The most common presenting symptoms of MM are fatigue and bone pain.[6] Anemia occurs in approximately 75% of patients and contributes to fatigue. Osteolytic skeletal lesions can be detected in approximately 80% of patients. Other common findings at presentation include hypercalcemia (15%) and elevated serum creatinine level (≥2 mg/dL) (20%).[6] Approximately 1% to 2% of patients with MM have extramedullary disease (EMD) at the time of initial diagnosis, and 8% have development of EMD later in the disease course.[20]

A monoclonal (M) protein in the serum or urine is a cardinal feature of MM but is seen in only 82% of patients on serum protein electrophoresis.[6] The sensitivity increases to 93% when serum immunofixation is added and to 97% with the addition of either the serum free light chain (FLC) assay or 24-hour urine studies.[21] Thus, if MM is suspected, the recommended screening strategy is serum protein electrophoresis, serum immunofixation, and either a serum FLC assay or 24-hour urinary protein electrophoresis with immunofixation. The M protein type is IgG in approximately 50%, IgA in 20%, immunoglobulin light chain only in 20%, IgD in 2%, and IgM in 0.5%.[6] About 2% to 3% of MM has no detectable M protein and is referred to as nonsecretory MM.[22]

The baseline diagnostic work-up required for the diagnosis of MM includes a complete blood cell count, measurement of serum calcium and creatinine levels, serum and urinary protein electrophoresis with immunofixation, serum FLC assay, and bone marrow examination. In addition, low-dose whole-body computed tomography or [18^F]-fluorodeoxyglucose–positron emission tomography/computed tomography or, at minimum, plain radiography of the entire skeleton are required to detect osteolytic bone lesions.[23] The osteolytic bone lesions in MM exhibit no new bone formation, and nuclear medicine bone scans are therefore not helpful.[24] Magnetic resonance imaging of the whole body or spine/pelvis is needed in patients with suspected SMM and whenever the diagnosis of MM is in doubt to look for focal bone marrow lesions.[25] Magnetic resonance imaging is also often needed in patients with osteolytic bone disease involving the spine to rule out cord compression and to determine the need for interventional procedures such as vertebroplasty or kyphoplasty.

DISEASE DEFINITION

In 2014, the International Myeloma Working Group updated the diagnostic criteria for MM and related disorders (Table 1).[1] The main revision was to add 3 highly specific biomarkers (clonal bone marrow plasma cells ≥60%, serum FLC ratio ≥100, and >1 focal lesion on magnetic resonance imaging) to existing markers of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) that were used to diagnose the disease. The updated criteria represent a paradigm shift because they allow early diagnosis and initiation of therapy before end-organ damage. As shown on Table 1, the diagnosis of MM requires 10% or more plasma cells on bone marrow examination or a biopsy-proven plasmacytoma plus one or more myeloma-defining events. The major differential diagnosis of MM includes MGUS, SMM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.

MOLECULAR CLASSIFICATION

Although MM is still considered a single disease, it is in reality a collection of several different cytogenetically distinct plasma cell malignant neoplasms (Table 2).[26,27] On fluorescence in situ hybridization studies of the bone marrow, approximately 40% of MM cases are characterized by the presence of trisomies in the neoplastic plasma cells (trisomic MM), while most of the

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