Current Concepts of Clinical Management of Multiple Myeloma

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Introduction

Multiple myeloma (MM) is a neoplastic proliferation of B lymphocytes (B cells) with plasma cell differentiation. The clonal plasma cells (PC) proliferate in the bone marrow and often result in anemia, hypercalcemia, destructive bone (osteolytic) lesions, and renal insufficiency.[1] MM is a type of plasma cell dyscrasia that includes the benign monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma, AL amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy monoclonal gammopathy, and skin changes), and plasma cell leukemia (Table 1).[2] It is believed that most cases of MM are preceded by a phase of MGUS. MM can be associated with AL amyloidosis in about 10% of cases. Plasma cell leukemia (abundant circulating PC) represents the most aggressive clinical scenario of MM with very poor prognosis.[1,3,4]

MM accounts for 1% of all malignancies and 10% of all hematological malignancies with 3-4 cases per 100,000. The incidence is highest among African Americans, then Caucasians, and is least common among Asians. It affects more men than women, with a ratio of 3:2. The disease is more common in developed countries; this could be attributed to more readily available diagnostic testing and longer life expectancy. In the USA, the lifetime risk of MM is 0.6%. The American Cancer Society estimates that in the USA about 20,520 new cases of MM will be diagnosed during 2011.[5]

The history and understanding of MM evolved over a span of 150 years. Although the earliest evidence of myeloma dates back to Egyptian mummies, the first case report was published in 1850 in England. Otto Kahler published a review in 1889 and the disease became known as Kahler's disease in Europe.[3] Wright described plasma cell etiology

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TABLE 1. Plasma cell disorders

Multiple myeloma
Solitary plasmacytoma
MGUS
Primary (AL) amyloidosis
Plasma cell leukemia
POEMS (osteosclerotic myeloma)

against the popular belief that MM originated from the red marrow and also described the x-ray abnormalities in myeloma.[6]

Etiology

The cause of MM is unknown. Except for very rare familial cases, MM is an acquired disorder. It is believed that genetic defects in the B cells make these cells susceptible to the effect of environmental toxins. The genetic defects can last for years as a subclinical condition, MGUS, until an environmental change triggers the progression to a neoplastic myeloma. Examples of commonly believed environmental exposure that predispose to MM are ionizing radiation (MM occurred in atomic bomb survivors after several years), pesticides (MM is more common with agriculture occupation), and occupational exposure to metals (eg, workers in nickel refineries).[1]

Pathogenesis

The neoplastic PC originate from postgerminal center B cells as evidenced by somatic hypermutation and homing of the clonal PC to the bone marrow.[1] In the bone marrow, the clonal PC interact with the extracellular matrix and adhere to the stromal cells via cell-surface adhesion molecules, which in turn promote plasma cell proliferation. Some studies suggested that these clonal PC originate and are maintained by neoplastic stem cells; however, this is not a generally accepted hypothesis. The survival and proliferation of myeloma cells are dependent on interleukin-6 (IL-6) and several other cytokines like insulin-like growth factor and vascular endothelial growth factor. IL-6 is produced by the monoclonal PC and the marrow stromal cells. A high serum level of IL-6 in patients with active disease correlates with widespread disease and poor prognosis. Factors produced by the clonal PC mediate bone destruction, the major pathologic feature of MM. Myeloma-derived macrophage-inflammatory protein (MIP)-1α upregulates the expression of the receptor activator of nuclear factor kappa B ligand by bone marrow stromal cells, which activates osteoclasts.[7]

TABLE 2. Diagnostic criteria for MM and other plasma cell disorders

Monoclonal gammopathy of uncertain significance:
Serum M-protein is <3 g/dL, bone marrow clonal plasmacytosis <10% and no myeloma-related end organ damage
Asymptomatic or smoldering myeloma:
Serum M-protein is >3 g/dL or bone marrow clonal plasmacytosis >10% in the absence of myeloma-related end organ damage
Symptomatic myeloma:
Evidence of monoclonal gammopathy (any level of serum or urine M-protein + clonal plasmacytosis in the bone marrow, often >10%) with at least 1 myeloma-related end organ damage
Plasmacytoma:
Single area of bone or soft tissue involvement with clonal plasmacytosis with no evidence of myeloma-related end organ damage. Skeletal survey and MRI of spine and pelvis should be done to exclude other lytic lesions

The clonal PC may exhibit translocation of the Ig heavy chain gene on chromosome 14 with different genes. These include FGFR3 (fibroblast growth factor receptor 3) on chromosome 4, which is a gene encoding a tyrosine kinase receptor that controls cellular proliferation, the cell cycle–regulatory genes cyclin D1 on chromosome 11, cyclin D3 on chromosome 6, or the gene for the transcription factor c-MAF (a human proto-oncogene) on chromosome 16.[8]

Clinical Presentation

MM is a disease of elderly people with a peak incidence between the ages of 65 and 70 years and a median age of 68 years. It is rare under the age of 40, which accounts for only 3% of all cases. MM symptoms can range from being completely asymptomatic (= smoldering myeloma) to a severely disabling illness with multiple complications. Table 2 describes the diagnostic features of the different types of plasma cell dyscrasia, including MGUS and solitary plasmacytoma. The diagnosis of multiple myeloma should be considered in patients with unexplained normocytic anemia, renal insufficiency, hypercalcemia (with low/normal intact parathyroid hormone level), and lytic bone lesions. These major manifestations of myeloma are often represented by the acronym CRAB (Table 3).[9]

Bone pain is the most common presenting symptom in up to 70% of cases and is secondary to lytic bone lesions. The bone lesions are usually multifocal and more commonly involve the axial skeleton: the vertebral column, ribs, skull, pelvis, femurs, clavicles, and scapulae. These lesions start in the medullary cavity of the bones, progressively destroy the bony cortex, and can result in pathologic fractures. The characteristic feature of the bone lesions is a punched-out lytic appearance but it less commonly

TABLE 3. Cardinal clinical features of MM is summarized as an acronym of CRAB

C	High calcium: >11.5 mg/dL that is attributed to myeloma
R	Renal insufficiency: serum creatinine >2 mg/dL that is attributed to myeloma
A	Anemia: typically normocytic anemia <10 g/dL or < 2 g/dL from baseline
B	Bone lesions (lytic) seen in skeletal x-ray films (skeletal survey)

manifests as diffuse osteopenia. Formation of the destructive bone lesions is mediated by the release of cytokines from the malignant PC, including MIP-1α, which causes increased osteoclast activity and the other factors leading to inhibition of osteoblast function, both of which lead to pathologic lytic bone lesions and pathologic fracture, such as vertebral compression fracture. Neurological symptoms (radiculopathy and paraparesis) result from vertebral compression fracture.

Renal dysfunction is also a common presentation. Renal dysfunction is seen in up to one-half of the patients and advanced renal failure is seen in 25% of the cases. The etiology of renal dysfunction is primarily related to tubular damage by the monoclonal light chain (Bence–Jones protein). The normal mechanism of tubular reabsorption of light chains is overwhelmed by the excessive amount of light chains excreted through the tubules, resulting in overloading of the tubular cells and formation of tubular casts (cast nephropathy). Other contributing factors are hypercalcemia (tubular calcium deposition) and volume depletion (hypercalcemia-induced osmotic dieresis). Proximal tubular dysfunction (Fanconi syndrome) can also be seen with depletion of phosphate, potassium, and bicarbonate (= type II renal tubular acidosis). The finding of glomerular damage (manifested as albuminuria/nephrotic syndrome) should raise the suspicion for amyloidosis or light chain nephropathy.[10]

Hypercalcemia is the presenting feature in about 30%-40% of cases of MM. Hypercalcemia can be spurious because of binding of paraproteins with calcium. Thus, ionized calcium is often more accurate for assessment of hypercalcemia. Hypercalcemia causes nausea, headache, lethargy, polyuria, osmotic polydipsia leading to renal dysfunction, and renal stone formation.

Anemia is seen in up to two-thirds of patients with MM and is usually normocytic normochromic anemia. It is related to plasma cell proliferation, replacing the bone marrow. The excess production of cytokines, such as IL-6, results in an inhibition of normal hematopoiesis. The eythropoietin level is often relatively low for the degree of anemia because of renal dysfunction.

Susceptibility to infection is increased in patients with MM. Risk of bacterial infection is related to hypogammaglobulinemia. Recurrent infections can predate the diagnosis of multiple myeloma. Common

infections are respiratory tract infections from streptococcus and staphylococcus and urinary tract infections due to Escherichia coli. During the treatment of myeloma, the risk of viral and fungal infection is also increased because of the use of systemic steroid therapy and other drugs that suppress lymphocyte production (bortezomib). Overwhelming infection is a common cause of death in MM.

Hyperviscocity is rare in MM and is more frequently seen in the IgA subtype because the IgA paraprotein has a higher tendency to form polymers. Hyperviscosity results in impaired cerebral circulation (headache, blurry vision, altered mental status), renal circulation (renal dysfunction), and pulmonary circulation (hypoxemia). Hyperviscosity also increases the risk of bleeding. This acquired coagulopathy is attributed to the interaction of M protein with clotting factors (I, II, V, VII, and VIII) and inducing platelet dysfunction.

Plasmacytomas are often seen in patients with MM. They can be bony or soft tissue tumors with local symptoms, such as pain, neuropathy, bleeding (gastrointestinal tract), airway obstruction (dysphonia and suffocation), or respiratory complication (lung masses). Patients with significant plasmacytoma burden can have tumor fever. Huge splenomegaly (because of plasmacytosis) is rarely seen in myeloma.

Peripheral neuropathy (sensorimotor) is sometimes seen in patients with MM because of myelin-associated antibodies. This can be associated with significant neuropathic pain requiring medical treatment. The presence of significant neuropathy (sensory or motor) should prompt a workup to assess for AL amyloidosis (often causes renal and/or liver dysfunction, heart failure because of left ventricular thickening with diastolic dysfunction, and gastrointestinal dysfunction). Progressive motor neuropathy should alert the physician to evaluate for POEMS syndrome (always associated with either sclerotic bone lesions or Castleman disease of the lymph nodes).

Amyloidosis (AL type) is seen in about 10% of cases and it often manifests as heart failure (diastolic dysfunction with thickened left ventricular wall and often normal left ventricular ejection fraction), renal insufficiency (with albuminuria and peripheral edema), gastrointestinal dysfunction (diarrhea), hepatic dysfunction, peripheral neuropathy, and tissue infiltration (macroglossia, joint pain).

Diagnosis and Workup

A cardinal feature of MM is the finding of monoclonal protein (M protein) seen in serum protein electrophoresis (SPEP) implying the clonality of the proliferating PC. The pathologic diagnosis of MM is made by finding clonal plasmacytosis in the bone marrow $\geq$10% of the marrow

cellularity or M-protein ≥3 g/dL. In rare scenarios, the diagnosis of MM is made without either criteria, in which case there should be pathologic evidence of extramedullary clonal plasmacytosis and other CRAB features (Table 3) that are attributed to plasmacytosis. Solitary plasmacytoma (either bony or soft tissue) is only diagnosed in the absence of CRAB features and a lack of pathologic diagnostic features of MM. MGUS is diagnosed when there is marrow clonal plasmacytosis <10% or M-protein <3 g/dL with the absence of CRAB features.

Once the diagnosis of multiple myeloma is suspected, the following workup is indicated:

- Complete blood picture: anemia and less often thrombocytopenia and neutropenia are seen. Anemia is typically normocytic normochromic, but can be macrocytic. Peripheral smear classically shows rouleaux formation of the red blood cells and can also show cryoglobulinemia. PC are sometimes seen in the peripheral blood and, if the circulating PC are greater than 2000/mm^2, the disease is classified as PC leukemia.
- Erythrocyte sedimentation rate and C-reactive protein can be elevated. Erythrocyte sedimentation rate can be >100 with a high concentration of paraprotein. Despite extensive bone lesions, the serum alkaline phosphatase is typically normal because of the absence of osteoblastic activity. Elevated alkaline phosphatase should raise the suspicion of other etiologies, such as liver disease, including hepatic amyloidosis or vitamin D deficiency.
- SPEP with immunofixation should be evaluated at baseline and with subsequent disease evaluations. M-protein is IgG in about 55% of cases, IgA in 20%. About 15%-20% of MM will have negative SPEP as the M-protein is a free light chain (kappa or lambda). Other rare subtypes are IgD and IgE and biclonal. IgM myeloma is very rare as IgM gammopathy is typically associated with lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia).
- A 24-hour urine protein electrophoresis (UPEP) is indispensable at the initial diagnosis of any case of multiple myeloma. UPEP can detect free light chain myeloma (often with negative SPEP). The excretion of free light chain in the urine (= Bence--Jones protein) is used for response assessment. Urine dipstick test does NOT detect Bence--Jones protein, but it is a rather sensitive test for albuminuria. The evaluation of the 24-hour urine albumin excretion is an essential test for the initial evaluation of all M cases. Albuminuria is a marker of glomerular injury. The finding of significant albuminuria should raise the suspicion of amyloidosis or light chain deposition disease. In

TABLE 4. International staging system

Stage	β-2 Microglobulin (mg/L)	Serum Albumin (gm/dL)	Median Survival
I	<3.5 AND	≥3.5	5 yr
II	Not fitting stage I or III		3.5 yr
III	≥5.5		2.5 yr

patients with diabetes mellitus, renal biopsy is often indicated to distinguish the etiology of albuminuria.

- Serum free light chain test (SFL) is indicated in many situations. It is used to evaluate MM once M-protein is very low (<0.05 g/dL) as sensitivity of the SPEP declines significantly at this point. It is used to follow-up light chain deposition disease and patients with MM who secrete only light chain (often have very small M-protein that is difficult to quantify). SFL shows a faster response than SPEP and thus can be an early marker of disease response to therapy. It is estimated that only 1% of MM patients will have negative SPEP, UPEP, and SFL test, thus called true nonsecretory myeloma. Those nonsecretory cases are evaluated by the amount of clonal PC in the bone marrow.
- Serum albumin and β-2 microglobulin levels are essential for staging using the international staging system (Table 4). The β-2 microglobulin reflects the disease burden and is also elevated with renal insufficiency.
- Quantitative immunoglobulin level is routinely assessed in patients with myeloma. There is always reciprocal reduction of the uninvolved immunoglobulins.
- Skeletal survey (plain radiographic x-ray images) is obtained in all patients to assess for lytic lesions. Diffuse osteopenia can sometimes be due to extensive lytic lesions. The radioisotope bone scan is very insensitive for detection of lytic lesions as they are not associated with osteoblastic activity.
- Bone marrow biopsy and aspirate (unilateral) are required for the diagnosis of MM. It is generally indicated for patients with gammopathy if M-protein is non-IgG, if the IgG M-protein is >1.5 g/dL, or if myeloma is suspected regardless of the amount of M-protein. Routine assessment of Congo red stain of the biopsy is a good practice as amyloidosis should always be suspected with any case of MM. Karyotyping and fluorescence in situ hybridization testing should be done in all cases with MM to establish the cytogenetic risk level that impacts prognosis.

TABLE 5. Durie–Salmon staging system[a]

Stage I (all the following):
Calcium <12 mg/dL
Hemoglobin >10 g/dL
M-protein: IgG <5 g/dL, IgA <3 g/dL
No lytic lesions
Stage II: Not fulfilling criteria for Stage I or III
Stage III (any of the following):
Calcium >12 mg/dL
Hemoglobin <10 g/dL
M-protein: IgG >7 g/dL, IgA >5 g/dL
Multiple lytic lesions

[a]The staging is further classified as "*A*" if creatinine is <2 mg/100 mL and "*B*" if it is >2 mg/dL.

TABLE 6. The prognostic risk factors of multiple myeloma[a]

Poor Risk	Favorable Risk
Deletion 13 (del 13q14): by karyotyping.	• T(11;14)
• T(4;14)	• T(6;14)
• T(14;16)	Hyperdiploidy (extra is good!)
• T(14;20)	Normal and other cytogenetic abnormalities
Del 17p13 (P53 locus)	
Hypodiploidy (loss is bad!)	

[a]Translocations of IgH locus in chromosome 14 *is* a common cytogenetic feature.

Staging and Prognosis

Once the pathologic diagnosis of myeloma is established, it is essential to define if the disease is symptomatic, CRAB features (active myeloma), or smoldering (inactive myeloma) as per criteria in Table 2. The term indolent myeloma has been redundantly used in the past to describe very slowly progressive active disease or inactive disease.

Active myeloma is classified according to 2 staging systems. These are the Durie–Salmon staging system and a more recently adopted international staging system. The Durie–Salmon staging system accounts for the degree of anemia, renal dysfunction, calcium level, and the extent of bone involvement[11] (Table 5), while the international staging system is based simply on the serum β-2 macroglobulin level and albumin level[12] (Table 4).

It is imperative to note that the prognosis of MM relies not only on the staging but also to a large extent on the cytogenetic features[8] (Table 6).

Treatment

MM remains an incurable malignancy. Patients with smoldering myeloma are closely followed up (1-2 months) to monitor for anemia, renal insuffi-

TABLE 7. Treatment regimens for MM that are commonly used as upfront or salvage setting

Transplant eligible
Lenalidomide/dexamethasone
Bortezomib/dexamethasone
Bortezomib/lenalidomide/dexamethasone
Bortezomib/cyclophosphamide/dexamethasone
Thalidmide/dexamethasone
Non-transplant eligible
Melphalan/bortezomib/dexamethasone
Melphalan/thalidomide/dexamethasone
Lenalidomide/dexamethasone

TABLE 8. The International Myeloma Working Group Response Criteria of multiple myeloma (simplified)

CR: complete disappearance of the M-protein and normal plasma cell percent in the bone marrow
sCR: same as CR with normal SFL ratio
VGPR: M-protein is detectable only by immunofixation (not by SPEP or UPEP) or at least 90% reduction in serum M-protein
PR: At least 50% reduction of serum M-protein
SD: neither response nor progression criteria
PD: increase by at least 25% of serum M-protein

CR, complete response; sCR, strict complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

ciency, and hypercalcemia, with bone survey performed once a year as a routine surveillance. Patients with solitary bone or soft tissue plasmacytoma (with no evidence of CRAB features of myeloma) are treated with radiation therapy. Surgical resection of solitary plasmacytoma is usually performed for initial diagnosis. Treatment of patients with plasma cell leukemia and AL amyloidosis is similar to treatment of active MM, but with special considerations. Management of these patients should be carried out ideally in centers with specialized expertise in this disease.

The outcome of myeloma treatment has been improved over the past decade by the use of the novel agents, bortezomib, lenalidomide, and thalidomide.[13]

Several regimens are available for the treatment of active MM in the initial and relapsed setting (Table 7). The response rate is 80%-90% in frontline therapy and 40%-60% in the first relapse setting, and poorer response is expected with subsequent relapse. Table 8 highlights the response criteria currently used to assess disease status during treatment.[9]

General practitioners are encouraged to be familiar with the common side effects of commonly used antimyeloma drugs (Table 9). The

TABLE 9. The side effects of the drugs used in treatment of active myeloma

Drug	Side Effects
Steroid	Infection
Dexamethasone	Worsening of diabetes and hypertension
Prednisone	Neuropsychiatric manifestation
	Osteoporosis
Alkylating agents	Myelosuppression
Melphalan	Immunosuppression
Cyclophosphamide	Stem cell damage (melphalan).
Immunomodulating drug (iMID)	Lenalidomide: myelosuppression,
Lenalidomide	thromboembolic complications
Thalidomide	Thalidomide: painful sensory neuropathy,
Pomalidomide (investigational and likely to be approved soon)	thromboembolic complications, cardiac arrhythmia
Proteasome inhibitor	Bortezomib: painful sensory neuropathy,
Bortezomib	shingles flare
Carfilozomib (investigational and likely to be approved soon)	
Anthracycline	Main toxicity: cadiotoxicity (less
Doxorubicin	pronounced with liposomal
Liposomal doxorubicin	doxorubicin) and myelosuppression

prescription of thalidomide and lenalidomide is available in the USA only through special Food and Drug Administration mandated programs to ensure avoidance of the teratogenic complications of these drugs.

The following guidelines generally apply to the initial treatment plan[14-16]:

- Steroid use is pivotal in the treatment of MM, thus is generally included in all treatment regimens.
- The incorporation of bortezomib in the initial treatment regimen is essential in patients with high-risk cytogenetic features.
- All patients receiving bortezomib should receive antiviral prophylaxis for shingles during treatment and for 6 months thereafter.
- Treatment is continued as long as there is a continued response and no significant toxicity.
- All patients receiving immunomodulatory agents (lenalidomide or thalidomide) should receive anticoagulation or antiplatelet agents (low-dose aspirin).

The choice of frontline regimen for patients with active MM depends on their eligibility for high-dose chemotherapy and autologous progenitor (stem) cell transplant (ASCT).[14,15] In patients who are eligible for ASCT, the use of the alkylating agent melphalan should be avoided as it can induce progenitor cell damage with subsequent failure to mobilize those

TABLE 10. Supportive care of patient with myeloma

Bone lesions:
Bisphosphonates (pamidronate and zolendronic acid)
Vertebroplasty or kyphoplasty.
Radiation therapy
Orthopedic fixation
Hypercalcemia:
Intravenous fluids
Bisphosphonates
Calcitonin
Gallium nitrate
Anemia (symptomatic)
Erythropoietin treatment or transfusion.
Infection
Intravenous immunoglobulin with repeated severe infections
Antiviral prophylaxis (acyclovir) during bortezomib treatment
Hyperviscosity
Plasmapheresis will be indicated with symptomatic hyperviscosity or severe renal failure due to very high free light chain
Thromboembolic prophylaxis (with iMID therapy)
Low-dose aspirin
Anticoagulation

cells for transplantation. ASCT can be used after initial induction treatment as an upfront approach or as salvage for relapsed disease. The primary benefits of ASCT are as follows:

- Prolongation of remission duration (average of 3 years vs 1-2 years with nontransplant regimens); this can be further prolonged by the increasing use of maintenance lenalidomide after transplant.
- Prolongation of overall survival for at least 1 year.
- Avoidance of high-grade toxicity of continued treatment.

Allogeneic progenitor (stem) cell transplant can be used in selected patients who are young with high-risk cytogenetic features and have a matched sibling. This is the only treatment that can potentially cure myeloma or induce long-term remission for >10 years.

Supportive Care

Supportive care is an integral part of the management of MM patients[16] (Table 10). Myeloma patients are susceptible to consequences caused by the disease or treatment. The following are common considerations:

- Painful bone lesions: kyphoplasty or vertebroplasty can be done for a compression fracture to restore vertebral height with quick improvement of pain. Radiation treatment is used for nonvertebral lesions or if

these procedures are not feasible. Orthopedic fixation can be used for impending or actual pathologic fracture. The use of bisphosphonates diminishes the risk of skeletal complications. Patients should be counseled on the risk of osteonecrosis of the jaw during bisphosphonate treatment and should have serial dental assessment during this therapy. The use of nonsteroidal anti-inflammatory drugs is strongly discouraged to avoid renal injury.

- Hypercalcemia is usually controlled by intravenous fluids, steroids, and bisphosphonates. Refractory cases may require calcitonin injections or rarely gallium nitrate.
- Infection: Patients with severe hypogammaglobulinemia are susceptible to recurrent infection of either systemic (low IgG) or the upper respiratory tract (low IgA). Prolonged antibiotic use can be used for prophylaxis. Intravenous immunoglobulin is used with recurrent severe infections. Antiviral prophylaxis is used with bortezomib therapy.
- Anemia: Erythropoietin use can be considered. Overcorrection of anemia will impose a risk of thromboembolic complications particularly in patients receiving iMID drugs.

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