Multiple Myeloma: Updates in Management

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Introduction

Multiple myeloma (MM) is a hematologic malignancy of the plasma cell that is characterized by increased secretion of monoclonal immunoglobulins (M-protein) in the bone marrow.

Accumulation of malignant plasma cells results bone destruction.

- Advancement in the treatment of MM have been numerous and survival rate is increased, in recent few yrs.

- Combination therapy of proteaosome inhibitors, an immunomodulatory drug and dexamethasone is widely accepted as first line therapy.

- Autologous SCT remain fundamental of the management of MM, although allogenic SCT is being considered for selected patients.F

Epidemiology

- MM accounts for

  1% of all malignancies;

  10% of haematological malignancies.
- Incidence: ~ 4 per 100,000 per annum.
- Age : Median age 66 years;

  <3% <40 years.
- Sex: M: F= 1.5:1.
- Race: Afro-Caribbeans > Caucasians; (2 ×)

  Lowest in Asians.
- Familial clusters have been reported, suggesting a possible genetic element.

Etiology and Pathogenesis

- MM arises from a terminally differentiated postgerminal center plasma cell.
- The pathogenesis of myeloma is complex, and many steps in the pathway are not fully elucidated.
- Most cases of MM are preceded by the premalignant asymptomatic states of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM).
- 1% of MGUS turns into MM annually.
- 10% of SMM terns into MM annually.
- Over all 73% of these group terns into MM in 15yrs.

- Myeloma is a heterogeneous disease that is based on various genetic aberrations.

- Many of the chromosomal abnormalities include translocations in the immunoglobulin-heavy chain of chromosome 14, aberrations in chromosomes 1, 5, 13, and 17, and trisomies.

- MM development is affected by changes in adhesion molecule expression and subsequent interactions within the complex microenvironment of the bone marrow, which induces cytokine and growth factor secretion.

- Various cytokines, including interleukin-6, interleukin-10, and insulin-like growth factor, are produced and secreted by myeloma and other cells within the bone marrow and promote proliferation of malignant cells.

Signs and Symptoms

- The hallmark clinical features of MM—Hypercalcemia, Renal insufficiency, Anaemia, and Bone lesions—are often remembered by the mnemonic CRAB.

- Most MM patients are symptomatic upon diagnosis;
  - 33% of cases present with renal insufficiency
  - 75% have anaemia commonly accompanied by fatigue,
  - 80% have bone lesions, which can be identified on x-ray or MRI.

- Patients may also experience recurrent infections or weight loss.

- Rarely, patients may present with hyper viscosity syndrome, like;
  - Headache
  - Blurred vision
  - Epistaxis
  - Oral bleeding
  - Altered mental status or confusion.

CRAB Criteria Used in the Diagnosis of MM

Feature	Symptom	Diagnostic Criteria	Management
C	Calcium	Corrected serum calcium >11 mg/dL	Hydration and IV bisphosphonates; additional agents include corticosteroids and calcitonin
R	Renal insufficiency	SCr >2 mg/dL	Correct hypercalcemia and possible dehydration. Avoid nephrotoxic agents such as NSAIDs
A	Anemia	Hemoglobin <10 g/dL or >2 g/dL below LLN	Correct iron, folate, and vitamin B_{12} deficiency. If patient is symptomatic, consider use of an erythropoietic agent; however, recognize that myeloma therapy may increase risk of thrombosis
B	Bone disease	One or more osteolytic lesions, pathological fractures, severe osteopenia, and/or pain	Bisphosphonates or denosumab for lytic bone disease; pain control may be necessary

LLN: lower limit of normal; MM: multiple myeloma; NSAIDs: nonsteroidal anti-inflammatory drugs; SCr: serum creatinine.
Source: References 5, 9, 10.

Diagnosis

Diagnostic criteria for MM

- Monoclonal protein in serum and/or urine (*Note*: no minimum level).
- Clonal BM plasma cells (*Note*: no minimum level; 5% have <10% plasma cells) or plasmacytoma.
- Myeloma-related organ or tissue impairment (*acronym* 'ROTI')
  - Elevated Ca^{2+} levels: serum Ca^{2+} >0.25mmol/L (>1mg/dL) above upper limit of ↔ or corrected serum Ca^{2+} >2.75mmol/L (>11mg/dL).
  - Renal insufficiency: (creatinine >173 micromol/L or >2mg/dL).
  - Anemia: Hb 2g/dL below ↔ range or Hb <10g/dL.
  - Bone lesions: lytic lesions or osteoporosis with compression fractures recognized by conventional radiology.
  - Others: symptoms of hyperviscosity; amyloidosis; recurrent bacterial infection.

Diagnosis cont'd

- The 2014 IMWG guidelines include three new biomarkers for patients without CRAB features, including clonal bone-marrow plasma cell percentage of 60% or greater, serum free light chain ratio 100 mg/mL or higher, and one or more focal lesions that are 5 mm or greater on MRI studies.

- A detailed medical history and physical examination, bone-marrow biopsy, radiography, and laboratory testing are important components of diagnosis.

Staging and Prognosis

- The International Staging System (ISS), published in 2005, is a simple tool that correlates MM prognosis and survival.
- Criteria for the three stages are based on levels of serum beta-2-microglobulin and albumin.
- Over the past decade, the understanding of cytogenetics and its influence on survival have added to the prognostic factors for myeloma, which were lacking in the original ISS.
- In 2015, the IMWG published a revised ISS that incorporates cytogenetic factors and lactate dehydrogenase—a marker reflective of tumor burden—to the original ISS definitions of stage.

R-ISS for MM

Stage	Criteria	Survival (mo)
I	• β_2-microglobulin <3.5 mg/L • Albumin ≥3.5 g/dL *and* • Standard-risk chromosomal abnormalities *and* • Normal LDH (defined as less than ULN)	82
II	• Not R-ISS stage I or III	62
III	• β_2-microglobulin ≥5.5 mg/L regardless of albumin levels *and* • High-risk chromosomal abnormalities: del 17p, t(4;14) or t(14;16) *and* • High LDH (defined as higher than ULN)	40

del: deletion; LDH: lactate dehydrogenase; MM: multiple myeloma; R-ISS: Revised-International Staging System; t: translocation; ULN: upper limit of normal.
Source: References 5, 11.

Treatment

- Although MM is currently incurable, the primary goal is to achieve a deep, long-lasting response. Therapy should control disease, minimize complications, and improve quality of life.
- Myeloma treatment depends on whether the patient is symptomatic or not.
- Patients with MGUS and SMM are usually observed, and treatment is initiated upon disease progression to active MM.
- This treatment is patient-specific and depends on numerous factors, including cytogenetics, disease stage, age, comorbidities, and performance status.

- MM treatment involves primary therapy and assessment of SCT eligibility. Primary therapy will be followed with high-dose (HD) chemotherapy and autologous SCT and/or maintenance therapy in selected patients.

- Allogeneic SCT may be considered in selected patients, although data comparing outcomes with those for autologous SCT are lacking.

- Regardless of transplantation status, all patients receive primary therapy with a two- or three-drug combination of an immunomodulatory agent, corticosteroid, and Proteasome Inhibitor (PI).
- The NCCN guidelines prefer a triple-drug regimen based on increased response rates, deeper responses, and increased over all survival compared with two-drug regimens.
- Two-drug regimens are reserved for frail patients and those who cannot tolerate a three-drug regimen.
- The newer novel drugs daratumumab and elotuzumab provide additional options for patients with relapsed/refractory disease.

- Primary therapy is used to reduce tumor burden and resolve the complications of MM.
- Following a response to primary therapy, transplant-eligible patients will undergo autologous SCT and may follow up with lenalidomide or bortezomib maintenance therapy.
- In transplant-ineligible patients, the selected regimen is typically continued until disease progression occurs; when this takes place, another regimen for relapsed disease is initiated.

PIs: These agents are the backbone of many MM regimens. Currently, three PIs are commercially available:

- ❑ Bortezomib
- ❑ Carfilzomib
- ❑ Ixazomib.

Immunomodulatory Drugs: Immunomodulatory drugs are often added to the PI base. Commonly used drugs are;

- ❑ Thalidomide,
- ❑ Lenalidomide,
- ❑ Pomalidomide

Corticosteroids: A corticosteroid—specifically, DXM—is added to almost all primary and relapsed/refractory myeloma regimens.

- Additional Agents: Increased understanding of myeloma and the microenvironment has led to a plethora of novel antimyeloma drugs.

- Two monoclonal antibodies (Mabs) have been added to the antimyeloma armamentarium for relapsed/refractory MM.

  - Daratumumab (Darzalex)
  - Elotuzumab (Empliciti)

- Panobinostat (Farydak) is an oral pan-deacetylase inhibitor used in combination with bortezomib and DXM.

Supportive Care

- Supportive care is a necessary component of MM management.
- Adjunctive medications can improve quality of life and minimize CRAB feature–associated complications.
- Because bone lesions are a hallmark characteristic of MM, denosumab or IV bisphosphonates—either zoledronic acid or pamidronate—are recommended for all patients with symptomatic MM.
- Patients should have a dental examination prior to starting bisphosphonate therapy and be monitored routinely for osteonecrosis of the jaw.
- In addition to skeletal-lesion prevention, the other complications of CRAB should be appropriately managed .
- Thromboprophylaxis should be considered when patients are on an immunomodulatory drug combination, and herpes prophylaxis with an antiviral is required for patients receiving daratumumab or a PI.

THANK YOU