

Navigating the Landscape of Multiple Myeloma: Classification, Staging, and Modern Therapeutics

Authors:

Dr. Mehak Parray¹, Dr. Faiza Mushtaq², Dr. Zarkah Nabi³, Dr. Era Hans⁴, Dr. Nazia Tabassum⁵, Dr. Parveen Shah⁶

^{1,2}Senior Resident, GMC Anantnag.

³Ex Senior Resident, GMC Anantnag.

⁴Assistant Professor, GMC Jammu.

⁵Consultant GMC Doda.

⁶Ex HOD GMC Baramulla.

Corresponding Author:

Dr. Zarkah Nabi, Ex Senior Resident, GMC Anantnag.

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ABSTRACT

Background: Multiple myeloma (MM) is a clonal plasma-cell neoplasm that can cause end-organ injury through bone disease, anemia, renal impairment, and hypercalcemia. Diagnosis and management have changed with the use of sensitive imaging, cytogenetic and molecular testing, and treatments directed at plasma-cell biology. **Scope:** This narrative review summarizes the biological basis and clinical presentation of MM, the diagnostic criteria used to distinguish active disease from precursor conditions, and the role of staging and cytogenetic risk assessment. It then reviews treatment principles for newly diagnosed and relapsed/refractory disease, including transplantation, maintenance therapy, supportive care, and newer immune-based treatments. **Review Approach:** The manuscript draws on a selective PubMed literature search covering 2008–2024 and on relevant clinical guidelines. It is a narrative review rather than a systematic review: the source manuscript does not report a reproducible full search strategy, predefined eligibility criteria, duplicate screening, or formal risk-of-bias assessment. **Conclusion:** MM management now combines clinical assessment with cytogenetic risk, response monitoring, and treatment tailored to disease setting and patient fitness. Immunotherapies have expanded options for relapsed disease, while measurable residual disease assessment is increasingly used to describe depth of response. The evidence and availability of individual therapies continue to change, so treatment choices should be checked against current guidelines.

Keywords: Multiple myeloma; Plasma cell neoplasms; Cytogenetic abnormalities; International Staging System; Risk stratification; Immunotherapy; Chimeric antigen receptor T-cell therapy; Bispecific antibodies; Minimal residual disease; Autologous stem cell transplantation.

INTRODUCTION

Plasma cell neoplasms are monoclonal expansions of a single late-stage post-germinal centre B lymphocyte which are class switched and terminally differentiated B cells having the predisposition to mature into plasma cells. All the differentiated cells within the neoplasm secrete monoclonal immunoglobulin chain or chain fragment known as M protein or para-proteins. In a particular neoplasm, the monoclonal proteins generally have the same heavy-chain class ($\alpha, \mu, \gamma, \delta$), or same light-chain class (λ, κ).¹ This review is organized around the clinical pathway from recognition of a plasma-cell disorder to diagnosis, risk assessment, and treatment. It emphasizes how staging and cytogenetic findings inform management and summarizes established treatment approaches alongside newer immune-based options. It does not attempt a systematic comparison of treatment efficacy across trials. Multiple myeloma is a neoplastic plasma cell disorder defined by a clinical pentad of: (a) anemia, (b) a monoclonal protein in the serum or urine or both, (c) abnormal bone radiographs and bone pain, (d) hypercalcemia, and (e) renal abnormalities or renal failure. The term ‘multiple myeloma’ was coined in 1873 by von Rustizky³, who independently described a patient emphasizing multiple bone tumors. Henry Bence Jones² first discovered monoclonal light chains in the urine of

myeloma patients. Samuel Solley reported the first well-documented case of myeloma in Sarah Newbury in 1844 (termed ‘mollities ossium’).⁴

Plasma cell neoplasms include:

Plasmacytoma

- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma

Plasma cell myeloma

- Plasma cell myeloma
- Clinical variants
 - Smouldering(asymptomatic) myeloma
 - Non-secretory myeloma
 - Plasma cell leukemia

Plasma cell neoplasms with associated paraneoplastic syndrome

- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes)
- Also termed osteosclerotic myeloma-characterized by a chronic/sub acute sensorimotor polyneuropathy with predominating motor disability.⁵
- TEMPI syndrome (telangiectases, elevated erythropoietin and erythrocytosis, monoclonal

gammopathy, peri-nephric fluid collection, and intrapulmonary shunting)-characterised by unexplained erythrocytosis (JAK2 negative), monoclonal gammopathy, peri nephric fluid collections, telangiectasias seen mostly on face, upper back and chest.

- AESOP syndrome (adenopathy, and extensive skin patch overlying plasmacytoma)- consisting of solitary plasmacytoma, slow growing red brown skin patches and associated desquamation characterised by diffuse reactive vascular hyperplasia within dermis.

In addition a number of conditions produce M proteins and paraproteins in the form of monoclonal immunoglobulins, light chains, heavy chains, misfolded immunoglobulins. These conditions can range from asymptomatic precursor conditions (IgM and non-IgM MGUS), smouldering myeloma to symptomatic conditions which need proper treatment.

PATHOPHYSIOLOGY AND CYTOGENETICS

Multiple myeloma and precursor diseases probably originate when plasma cells divide in response to antigenic stimulation and subsequent cytogenetic abnormalities (hyperdiploidy and IGH translocations). IGH translocations involve the immunoglobulin heavy chain switch region on chromosome 14q32, and associated chromosome loci : CCND1(11q13), FGFR3 and NSD2(4p16.3), CCND3(6p21), MAF(16q23) and MAFB(20q11). Hyperdiploidy is characterized by trisomies of odd numbered chromosomes (3,5,7,9,11,15,19,21) and is considered an early event associated with a more indolent course and slower progression from MGUS. The progression to malignancy require development of additional second hit events and changes in tumor microenvironment, immune dysfunction and clonal evolution which underlies disease progression and therapeutic resistance. An important thing worth noting is that plasma cell neoplasms need not to go through all the stages in a particular order as some patients may directly advance to the malignant stage of the disease from MGUS without a frank SMM stage.

Plasma cell myeloma/Multiple myeloma shows characteristic plasma cells in the bone marrow which progressively tend to displace the normal marrow cells. The stromal cells and non-hematopoietic cells of multipotent lineage help in both development and progression by regulating cell migration, homing and angiogenesis. Clonal heterogeneity contributes to disease dissemination. Progression from precursor states to multiple myeloma involves novel mutations, biallelic hits in tumor suppressor genes, driver gene mutations influencing cell signalling pathways such as RAS/MAPK and NF-κB pathway activation, DNA repair pathway and MYC (translocations or copy number variations) which are considered to be secondary or late events. Copy number alterations like gain/Amplification of 1q (CKS1B, PSMD4) are powerful adverse prognostic markers. Deletion 17p (TP53 locus) and Deletion 13q/Monosomy 13 are also associated with chemoresistance. Somatic mutations activate key oncogenic pathways like MAPK pathway (KRAS, NRAS, BRAF mutations), NF-κB pathway (TRAF3, CYLD, NFKB1/2), DNA repair pathway (TP53

mutations often biallelic with del 17p) and MYC dysregulation.^{6,7,8}

The bone marrow microenvironment is an important active participant in myeloma pathogenesis, providing proliferative signals, conferring drug resistance and suppressing immunity.²⁵ Mesenchymal stromal cells adopt a pro-inflammatory, cancer associated fibroblast phenotype secreting survival signals (IL-6, IGF-1, VEGF, SDF-1α). Osteoclasts become hyperactivated via RANKL/OPG imbalance leading to bone destruction and releasing bone embedded growth factors like TGF-β, IGF-1 causing a vicious cycle of bone resorption and tumor growth. Osteoblasts are suppressed by factors secreted by myeloma cells like sclerostin, DKK1 and other Wnt pathway inhibitors leading to impaired bone formation.^{6,7,8}

Myeloid derived suppressor cells, tumor associated macrophages and regulatory T cells create an immunosuppressive niche that inhibit cytotoxic T-cell and NK-cell function. In addition myeloma cells induce a hypoxic microenvironment, upregulating HIF-1α, glycolysis and drug resistance. Immune dysfunction and evasion occurs leading to impairment of immune surveillance by upregulation of inhibitory receptors (PD-1, TIM-3, LAG-3) on T cells.

CLINICAL FEATURES

Multiple myeloma can have a heterogeneous presentation varying from asymptomatic premalignant stage called monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma to pleomorphic plasma cells detected in peripheral blood. Many of the patients at presentation show evidence of plasma cell myeloma related damage to one or more end-organ like hypercalcemia, renal insufficiency, anemia and bone lytic lesions. Hypercalcemia usually clinically manifests as polydipsia, polyuria, nausea, constipation, somnolence, confusion, and anorexia. Bone destruction is integrally present in MM and is seen in at least 70% of patients.⁹ Bone disease associated with MM may involve the extremities, but most frequently it involves the spine with characteristic exacerbation of the pain on movement and weight bearing. Some other features presenting in multiple myeloma include recurrent infections secondary to lymphocyte dysfunction, altered function of plasma cells and decreased immunoglobulin production. Hyperviscosity secondary to high level of circulating M-protein can also present rarely. Soft tissue swellings or organomegaly can be a presenting feature of Plasmacytomas. Plasmacytomas can occur in association with bony structures (medullary) or in other areas (extramedullary). The term solitary plasmacytoma is applied to tumor growth in patients with no other evidence of MM. Patients with plasmacytoma frequently present with back pain and a vertebral mass which needs a site-directed biopsy for diagnosis.

MICROSCOPIC EXAMINATION/ HISTOPATHOLOGY

MM is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.¹⁰ Peripheral smear may show abnormal distribution of RBCs such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.¹¹ Smear may also show myeloma cells in the circulation. The morphologic and immunologic phenotypes (bone marrow examination) of myeloma cells can be heterogeneous varying from mature appearing plasma cells to immature plasma cells, plasmablastic and pleomorphic forms. Mature plasma cells are approximately two to three times the size of

peripheral lymphocytes, having round to oval and eccentrically placed nucleus which contains characteristic clock face/spoke wheel chromatin. The displacement of nucleus from the centre is attributed to an abundance of rough-surfaced endoplasmic reticulum which is the site of immunoglobulin synthesis. The perinuclear clear zone called the perinuclear hof, is considered to be the site of Golgi apparatus functioning for packaging immunoglobulin and glycosylation followed by its secretion. Derangements of immunoglobulin secretion present in the form of flaming cells, Mott cells, Russell bodies, and Gaucher-like cells. Flaming cells are plasma cells that have intensely eosinophilic cytoplasm with prominent margins attributed to plugging of peripheral secretory channels by precipitated immunoglobulin/fragments (IgA myeloma). The term ‘Thesaurocytes’ is used for large flaming cells with a pyknotic nucleus that is pushed to the side. Mott cells (grape/morula cells) are plasma cells filled with dense immunoglobulin inclusions in a spherical configuration which can be colorless, pink, or blue. Additionally other inclusions include Russell bodies and intranuclear dense bodies that appear cherry red in colour. Gaucher-like cells are macrophages laden with sphingolipids released by the dying plasma cells¹². All of these inclusions are not specific for malignancy and have no prognostic value. Cases of myeloma having plasmablastic morphology have a diffuse chromatin pattern, less abundant cytoplasm, a central nucleus with little/no hof^{13,14}. Myeloma can have diffuse and nodular infiltration patterns and cells commonly present in cords around marrow vessels. The immunophenotype of myeloma cells is complex. In general, myeloma cells are CD45-, CD38+ and CD138+. CD56 is strongly positive in about 55 to 78% of myeloma cases.^{16,17,18} CD56-negative myeloma cells tend to be present in more aggressive disease, such as end-stage myeloma or PCL.^{18,19} Costimulatory molecules involved in the activation of B and T lymphocytes (CD28 and CD40) are seen in about 40 and 70% of patients, respectively.^{20,21} Immunohistochemistry/Flow cytometry is of utility in detecting and quantifying plasma cells (using CD138, CD38 and IRF4/MUM1), detection of κ and λ light chain light chain restriction/monoclonal proliferation. In addition Slam-family proteins like CD229 and CD319 are also positive. Abnormal expression during the course of disease can occur especially CD20, CD28, CD33, CD 10 and CD117(KIT).^{20,21}

DIAGNOSTIC WORK-UP

The diagnosis requires 10% clonal bone marrow plasma cells or a biopsy proven plasmacytoma plus evidence of one or more multiple myeloma defining events (MDE):

- ❖ CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) attributable to the plasma cell disorder,
- ❖ Bone marrow clonal plasmacytosis $\geq 60\%$,
- ❖ Serum involved/uninvolved free light chain (FLC) ratio ≥ 100 (provided involved FLC is ≥ 100 mg/L and urine monoclonal protein is ≥ 200 mg/24 h),
- ❖ or >1 focal lesion on magnetic resonance imaging.

The MM-defining biomarkers identified by the IMWG SLiM features (SLiM stands for sixty, light chain ratio, MRI) include one or more of the following: $\geq 60\%$ clonal plasma cells in the bone marrow; involved/uninvolved FLC ratio of 100 or more with the involved FLC being ≥ 100 mg/L; or MRI with more than one focal marrow (nonosteolytic) lesion.²⁴

Tests for patients presenting with a monoclonal gammopathy include the following:

- Hemoglobin and serum levels of calcium and creatinine
- Serum and urine protein electrophoresis and immunofixation
 - Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM);
 - Serum protein electrophoresis (SPEP) for quantitation of M protein; and
 - Serum immunofixation electrophoresis.Assessing changes in levels of various proteins, particularly the M protein, helps track disease progression and response to treatment.
- Quantitative immunoglobulins

The M protein is considered to be measurable if it is ≥ 1 gm/dl in the serum and or ≥ 200 mg/day in the urine. The M protein level is monitored by SPEP and serum FLC assay to assess treatment response every month while on therapy, and every 3–4 months when off-therapy. The serum FLC assay is particularly useful in patients who lack a measurable M protein, provided the FLC ratio is abnormal and the involved FLC level is ≥ 100 mg/L.²² Urine protein electrophoresis is recommended at least once every 3–6 months, to follow the urine M protein level as well as to detect other renal complications that may result in albuminuria. Response to therapy assessment and minimal residual disease (MRD) evaluation is based on the revised IMWG uniform response criteria.^{22,23}

- Diagnostic imaging/Metastatic bone survey:
 - MRI of spine
 - Bone densitometry
- Bone marrow examination (aspirate and biopsy)
 - Bone marrow immunohistochemistry
 - Bone marrow flow cytometry
- Tissue biopsy to diagnose extraosseous plasmacytoma and Congo red staining of bone marrow and abdominal fat pad for amyloidosis (with or without electron microscopy [EM])
- Gene expression profile (GEP)
 - Cytogenetics
 - FISH (t(4:14), t(14:16), t(11:14), Del 13, Del 17p, Del 1p (CDKN2C), 1q21 gain/amplification
- Additional/ Supplementary tests/investigations- CBC with differential, BUN, creatinine, electrolytes, LDH, calcium, albumin, β 2-microglobulin, and C-reactive protein, plasma cell labeling index, and circulating plasma cells.

Table 1: International myeloma working group updated criteria for the diagnosis of multiple myeloma²⁴

Disorder	Disease definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	All 3 criteria must be met: Serum monoclonal protein (non-IgM type) <3 gm/dl Clonal bone marrow plasma cells <10% ^a Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma	Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥3 gm/dl, or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10%–60% Absence of myeloma defining events or amyloidosis
Multiple myeloma	Both criteria must be met: Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma Any one or more of the following myeloma defining events: Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dl) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dl) Renal insufficiency: creatinine clearance <40 ml per minute or serum creatinine >177 µmol/L (>2 mg/dl) Anemia: hemoglobin value of >2 g/dl below the lower limit of normal, or a hemoglobin value <10 g/dl Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) Clonal bone marrow plasma cell percentage ≥60% Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L) >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)
Plasma cell leukemia	Both criteria must be met: Meets diagnostic criteria for multiple myeloma Presence of 5% or more plasma cells in conventional peripheral blood smear white blood cell differential count
IgM monoclonal gammopathy of undetermined significance (IgM MGUS)	All 3 criteria must be met: Serum IgM monoclonal protein <3gm/dl Bone marrow lymphoplasmacytic infiltration <10% No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.
Light Chain MGUS	All criteria must be met: Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio >1.65 and increased lambda FLC in patients with ratio <0.26) No immunoglobulin heavy chain expression on immunofixation Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells <10% Urinary monoclonal protein <500 mg/24 h
Solitary plasmacytoma	All 4 criteria must be met Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

Disorder	Disease definition
Solitary plasmacytoma with minimal marrow involvement ^b	All 4 criteria must be met Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells <10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

- Modified from Rajkumar et al.²⁴
- ^a A bone marrow can be deferred in patients with low risk MGUS (IgG type, M protein <15 gm/L, normal free light chain ratio) in whom there are no clinical features concerning for myeloma.
- ^b Solitary plasmacytoma with 10% or more clonal plasma cells is considered as multiple myeloma.²⁴

CYTOGENETIC/ MOLECULAR CLASSIFICATION (BY FISH)

Table 2. Primary molecular cytogenetic classification of multiple myeloma^{23,11}

Subtype	Gene(s)/chromosomes affected	Approximate percentage of myeloma patients
Hyperdiploid multiple myeloma ^a	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21	45
IgH translocated multiple myeloma		40
t(11;14) (q13;q32)	CCND1 (cyclin D1)	20
t(6;14) (p21;q32)	CCND3 (cyclin D3)	5
t(4;14) (p16;q32)	NSD2	10
t(14;16) (q32;q23)	C-MAF	4
t(14;20) (q32;q11)	MAFB	<1
Other IgH translocations, other cytogenetic abnormalities, or normal		

Modified from Kumar et al.²³

a Requires absence of an immunoglobulin heavy chain translocation. If an immunoglobulin heavy chain translocation is present, classification will be based on that abnormality.²³

Table 3. Cytogenetic abnormalities on clinical course and prognosis in multiple myeloma

Cytogenetic abnormality	Clinical setting in which abnormality is detected	
	Smoldering multiple myeloma	Multiple myeloma
Trisomies	Intermediate risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7–10 years
		Most have myeloma bone disease at diagnosis
		Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(6;14) (p21;q32)	Standard risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(4;14) (p16;q32)	High risk of	Intermediate-risk MM, median OS 5 years

Cytogenetic abnormality	Clinical setting in which abnormality is detected	
	Smoldering multiple myeloma	Multiple myeloma
	progression, median TTP of 2 years	Needs bortezomib-based initial therapy, early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
t(14;16) (q32;q23)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
		Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
Gain(1q21)	High risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
Del(17p)	High risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high-risk IgH translocations, and del 17p
Isolated Monosomy 13, or Isolated Monosomy 14	Standard risk of progression, median TTP of 5 years	Effect on prognosis is not clear
Normal	Low risk of progression, median TTP of 7–10 years	Good prognosis, probably reflecting low tumor burden, median OS >7–10 years

Note: Modified from Rajan and Rajkumar²⁶.

Table 4: Criteria for high-risk smoldering multiple myeloma²³

- The term smoldering multiple myeloma excludes patients without end-organ damage who meet revised definition of multiple myeloma, namely clonal bone marrow plasma cells ≥60% or serum free light chain (FLC) ratio ≥ 100 (plus measurable involved FLC level ≥ 100 mg/L), or more than one focal lesion on magnetic resonance imaging.
- The risk factors listed in this table variables associated with a higher risk of progression of SMM, and identify patients who need close follow up and consideration for clinical trials.
- Progressive increase in M-protein level(Evolving type SMM):-Increase in serum monoclonal protein by ≥25% on two successive evaluations within a 6-month period.²³

Mayo 2018 criteria
Any 2–3 of the following:
Serum free light chain ratio (involved/uninvolved) >20
Bone marrow plasma cells >20%
Other high-risk factors
Progressive increase in M protein level (Evolving type of SMM)
Bone marrow clonal plasma cells 50%–60%
t (4;14) or del 17p or 1q gain
Increased circulating plasma cells
MRI with diffuse abnormalities or with one focal lesion
PET-CT with focal lesion with increased uptake but without underlying osteolytic bone

Mayo 2018 criteria
destruction

HISTORICAL AND CONTEMPORARY STAGING SYSTEMS

DURIE SALMON STAGING SYSTEM (1975)

Durie-Salmon Staging^{27,28}

Stage I

- Hemoglobin value 10 g/dL
- Serum calcium value normal or =12 mg/dL
- Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only
- Low M-component production rate (IgG value <5 g/dL; IgA value <3 g/dL; Bence Jones protein <4g/24 hr)

Stage II

Neither stage I nor stage III

Neither stage I nor stage III

Stage III

On or more of the following:

- Hemoglobin value 12 mg/dL
 - Advanced lytic bone lesions (scale 3)
 - High M-component production rate – IgG value >7 g/dL; IgA value>5 g/dL; Bence Jones protein>12 g/24 h
- Durie-Salmon sub classifications (either A or B)
- A: Relatively normal renal function (serum creatinine value <2.0 mg/dL)
- B: Abnormal renal function (serum creatinine value =2.0 mg/dL)

INTERNATIONAL STAGING SYSTEM(ISS-2005)

Staging criteria

- Stage I: Serum β2-microglobulin < 3.5mg/L and Serum albumin>3.5 g/dL
- Stage II: neither Stage I nor Stage III(β2M< 3.5mg/L and albumin <3.5g/dL) or (β2M 3.5-5.5 mg/L).
- Stage III: Serum β2-microglobulin >5.5mg/L.³¹

REVISED INTERNATIONAL STAGING SYSTEM(R-ISS, 2015)

Revised International Staging System for Myeloma³⁰ Stage I

ISS stage I (serum albumin > 3.5, serum beta-2-microglobulin < 3.5) and
No high-risk cytogenetics
Normal LDH

Stage II

Neither stage I or III

Stage III

ISS stage III (serum beta-2-microglobulin > 5.5) and
High-risk cytogenetics [t (4;14), t(14;16), or del(17p)] or elevated LDH^{30,31,32,}

PROGNOSIS AND RISK STRATIFICATION

Molecular subtyping has emerged as a key in diagnosis and subtyping of multiple myeloma the presence or absence of secondary cytogenetic abnormalities such as del(17p), gain(1q), or del(1p).^{33,34} In addition to cytogenetic risk factors, two other markers that are associated with aggressive disease biology are elevated serum lactate dehydrogenase and evidence of circulating plasma cells on routine peripheral smear examination (plasma cell leukemia). The Revised International Staging System (RISS) combines elements of tumor burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level) to create a unified prognostic index that helps in clinical care as well as in comparison of clinical trial data (Table 5).³⁰ In order to ensure uniform availability, only three widely available cytogenetic markers are used in the RISS; the Mayo Clinic mSMART risk stratification (Table 6) has additional detail that is valuable in formulating a therapeutic strategy.³³

MODERN RISK STRATIFICATION

TABLE 4. Revised international staging system for myeloma³⁰

Stage
Stage 1 All of the following: Serum albumin ≥3.5 gm/dL Serum beta-2-microglobulin <3.5 mg/L No high-risk cytogenetics Normal serum lactate dehydrogenase level
Stage II Not fitting Stage I or III
Stage III Both of the following: Serum beta-2-microglobulin >5.5 mg/L High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated serum lactate dehydrogenase level

Table 6. Mayo clinic risk stratification for multiple myeloma (mSMART)³³

Risk group	Percentage of newly diagnosed patients with the abnormality
Standard risk	60%
Trisomies*	
t(11;14)	
t(6;14)	
High risk	40%
t(4;14)	
t(14;16)	
t(14;20)	
del(17p)	
gain(1q)	
Double-Hit myeloma: Any two high-risk factors	
Triple-Hit myeloma: Any three or more high-risk factors	

The presence of del(17p), t(4;14), t(14;16), t(14;20), gain 1q, del 1p, or p53 mutation is considered high-risk multiple myeloma. Presence of any two high risk factors is considered double-hit myeloma; three or more high risk factors is triple-hit myeloma.³⁴

TREATMENT: FROM STANDARD REGIMENS TO IMMUNE-BASED THERAPIES

Until recently, treatment of myeloma focused on the utility of cytotoxic agents (e.g. melphalan and cyclophosphamide) and corticosteroids (e.g. prednisone and dexamethasone). With the advancement in therapeutics, newer agents of myeloma treatment, have lead to a paradigm shift. Thalidomide is considered as one of the first of these drugs, was found to be effective in pretreated myeloma patients.^{35,36} It acts via an immunomodulatory mechanism. Thalidomide was then followed by bortezomib, which acts via proteasome inhibition.³⁶ It was followed by lenalidomide, an analogue of thalidomide but with more potent antimyeloma activity.³⁷ The advent and use of these novel agents have led to improved and enhanced overall survival which has been demonstrated by several groups.^{38,39}

APPROACH TO THERAPY

- **STANDARD THERAPY**
 - MGUS patients are closely monitored using the risk stratification model and observation with periodic monitoring (M protein, FLC ratio, cytogenetics).
 - Smoldering multiple myeloma (SMM): Close monitoring is done.
 - Newly diagnosed Multiple Myeloma: Treatment is stratified by transplant eligibility, which is primarily a function of age, performance status and comorbidities.
- Transplant eligible patients having a goal to achieve maximal depth of response by starting induction therapy by triplet or quadruplet regimens for 4-6 cycles.

- Autologous stem cell transplantation (ASCT): First line ASCT, Tandem ASCT(double autologous stem cell transplantation-patient undergoes two planned cycles of high dose chemotherapy followed by reinfusion of patients own stem cells).
 - Consolidation Therapy: Short term intensive treatment phase administered after patient has achieved adequate response from initial induction therapy with a goal to achieve complete response (CR) or minimal residual disease(MRD).⁴⁸
 - Maintenance Therapy: Lenalidomide is the main standard drug. High risk disease drug regimens include Bortezomib based maintenance, Carfilzomib based maintenance and Anti-CD-38 mAb-Daratumumab/Isatuximab maintenance.^{46,47,48,59}
 - Transplant ineligible patients are treated to achieve durable disease control with tolerable long-term therapy.
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- **Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)**
 - Treatment depends upon prior therapies, duration of response, aggressiveness of relapse and patient factors. Early relapse (first or second relapse) are challenged with triplet regimens.
 - Later relapses and triple class refractory disease (refractory to an IMiD, A PI, and an anti-CD-38 monoclonal antibody) are started with Bispecific T-cell engagers (TCEs)-Anti-BCMA (Teclistamab, elranatamab) and Anti-GPRC5D (Talquetamab) which act by redirecting host T-cells to kill myeloma cells.^{40,41,44,62}

- Chimeric Antigen Receptor T-cell (CAR-T) Therapy-Anti-BCMA (Idecabtagene vicleucel, Ciltacabtagene autoleucel) which act by targeting of BCMA by ex vivo genetic modification of patients T-cells.^{42,43}
- Other novel agents include Venetoclax (BCL-2 inhibitor), New generation Cereblon E3 Ligase Modulators (CELMods)⁵¹
- Supportive care includes use of bisphosphonates (Zoledronic Acid) or Denosumab (RANKL inhibitor) in monthly dose,
- Radiation Therapy/Vertebroplasty/kyphoplasty for palliative control of painful lesions.
- For managing renal symptoms hydration is advised alongwith use of steroids like dexamethasone.
- Infection prophylaxis includes specific antibiotics and vaccines especially inactivated ones.

IMMUNOTHERAPIES AND EMERGING TREATMENT APPROACHES

- Monoclonal antibodies: Daratumumab & Isatuximab (anti CD 38): First targeted antibodies for MM used in almost all phases of treatment.^{58,59}
- Novel targets include GPRC5D, FcRH5, CD229.⁵¹
- Next gen immunotherapy: Allogenic CAR-T, NK-cell therapies, bispecific antibodies with improved safety profiles.^{40-44,61,62}
- MRD-guided treatment cessation: Using MRD status and genomic profiling to guide duration and intensity of therapy.⁴⁸

TREATMENT PRINCIPLES AND SUPPORTIVE CARE

CAR T-cells are autologous or allogeneic T-cells transfected to express a cell surface receptor that recognizes one or more specific antigens on the surface of tumor cells, resulting in their activation, immunological synapse formation, and cytotoxic granule-mediated target cell apoptosis.⁴² The extracellular tumor antigen-binding domain consists of the variable regions of heavy (V_H) and light (V_L) chains of a monoclonal antibody, linked together by a peptide spacer to form a single chain variable fragment (scFv). The intracellular domains provide signal for T-cell activation via the CD3 ζ subunit of the T-cell receptor (TCR)-CD3 complex. First generation CAR constructs have the receptor and CD3 ζ alone. Second and third generation CAR T-cells have one or two co-stimulatory endodomains (e.g., 4-1BB, CD28) respectively which increase their potency. Further, CAR T-cells can be engineered to produce anti-tumor cytokines such as IL-12 after colocalizing with the tumor cell, thus limiting off-target toxicity.⁴³ CAR constructs have several-fold higher affinity for tumor cell surface antigens than naturally occurring TCRs. As scFvs can recognize intact cell surface proteins, CAR T-cells are not dependent on major histocompatibility complex (MHC)-mediated antigen presentation for activation.⁴⁴ CAR T-cells tested in MM can be categorized into BCMA and non-BCMA directed.^{40,41}

BISPECIFIC ANTIBODIES: BsAbs possess two antigen binding regions with different specificities. A bsAb is capable of binding to an antigen on the tumor cell and another antigen on an immune effector cell (e.g., T-lymphocyte) to redirect endogenous immune cells towards tumor cells, leading to immunological synapse formation, and tumor cell lysis.⁴⁰ BsAbs act independent

of MHC or TCR specificity. Since they do not require the ex vivo T-cell processing as in case of CAR T-cells, they substantially decrease the time to initiation of therapy.⁴² In its simplest form, a bsAb consists of a scFv for binding the target antigen on the tumor cell and another scFv for binding an immune effector cell, the two being connected by a linker peptide. This construct is called a bispecific T-cell engager (BiTE).⁴¹ Incorporation of an immunoglobulin Fc (fraction crystallizable) portion confers additional properties like antibody-dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity, and longer half-life in circulation. Tri- and tetravalent bsAbs can have additional binding sites incorporated for the same tumor antigen epitopes. Polyspecific Abs can target multiple tumor antigen epitopes to improve cell killing especially when the level of antigen expression is low.⁴⁰

Survival in multiple myeloma has improved significantly in the last 15 years.⁴⁵ The initial impact came from the introduction of thalidomide,³⁵ bortezomib,⁴⁶ and lenalidomide.^{47,48} In the last decade, carfilzomib, pomalidomide, ixazomib, elotuzumab, daratumumab, isatuximab, selinexor, belantamab mafodotin, and chimeric antigen receptor-T (CAR-T) cell therapies have been approved by the Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma, and promise to improve outcomes further. Thalidomide, lenalidomide, and pomalidomide are termed immunomodulatory agents (IMiDs). IMiDs bind to cereblon and activate cereblon E3 ligase activity, resulting in the rapid ubiquitination and degradation of two specific B cell transcription factors, Ikaros family zinc finger proteins Ikaros (IKZF 1) and Aiolos (IKZF3).⁴⁹⁻⁵¹ They may cause direct cytotoxicity by inducing free radical mediated DNA damage.⁵² They also have anti-angiogenic, immunomodulatory, and tumor necrosis factor alpha inhibitory properties. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors.⁵³⁻⁵⁵ Elotuzumab targets SLAMF7; daratumumab and isatuximab target CD38 respectively.⁵⁶⁻⁵⁹ Belantamab mafodotin is a humanized antibody targeting B cell maturation agent (BCMA) that is conjugated to monomethyl auristatin-F, a microtubule disrupting agent.⁶⁰ Idecabtagene vicleucel (ide-cel, bb2121) and ciltacabtagene autoleucel (cilta-cel) are newly approved CAR-T products targeting BCMA that are active in relapsed refractory myeloma.^{60,61,42}

The standard of care is complex and multi-phased involving induction regimens, consideration for transplantation, and prolonged maintenance. Furthermore, with the approval of immunotherapy agents of B cell maturation agent (BCMA) directed chimeric antigen receptor (CAR-T) cell therapies and bispecific T cell engagers are being considered as potent options for heavily pretreated patients. Yet Multiple myeloma remains incurable for many, with relapsing and remitting pattern dictated by clonal evolution and emergence of resistant subclones. The ultimate ambition is to transform multiple myeloma from a chronic relapsing condition into a curable disease.

Strengths of the Review

1. **Comprehensive Coverage:** The review covers the biological basis, clinical presentation, diagnostic criteria, histopathological features, cytogenetic classification, staging systems, prognosis, and contemporary treatment approaches for multiple myeloma.
2. **Integration of Diagnostic and Prognostic Parameters:** It discusses the role of bone marrow examination, immunophenotyping,

serum free light chain assays, fluorescence in situ hybridization (FISH), and molecular abnormalities in disease classification and risk assessment.

3. **Discussion of Established and Emerging Therapies:** The manuscript summarizes conventional therapeutic approaches and newer treatment modalities, including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, CAR T-cell therapy, and bispecific antibodies.
4. **Clinical Relevance:** The review highlights the importance of transplant eligibility, cytogenetic risk, treatment response, supportive care, and individualized therapeutic decisions.
5. **Coverage of Disease Heterogeneity:** The discussion of clonal evolution, the bone marrow microenvironment, immune dysfunction, and treatment resistance provides a useful overview of the biological mechanisms underlying disease progression.
6. **Educational Value:** The inclusion of diagnostic criteria, cytogenetic classifications, and staging systems may be useful for medical students, postgraduate trainees, pathology residents, and clinicians involved in the care of patients with plasma cell disorders.

Limitations of the Review

1. **Narrative Review Methodology:** The manuscript describes a selective literature search but does not provide a fully reproducible search strategy, predefined eligibility criteria, or a formal assessment of study quality.
2. **Limited Comparative Evidence:** The therapeutic discussion primarily summarizes available treatment approaches and does not systematically compare the efficacy, safety, or survival outcomes of different treatment regimens using quantitative evidence.
3. **Potentially Outdated References:** Several references are relatively old, and some sections require verification against the latest diagnostic classifications, clinical guidelines, and regulatory approvals for newer therapies.
4. **Limited Discussion of Treatment-Related Toxicities:** Adverse effects, treatment-associated infections, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and other complications of modern immunotherapies could be discussed in greater detail.
5. **Limited Economic and Accessibility Perspective:** The review does not extensively address treatment costs, availability of advanced therapies, or disparities in access to transplantation, molecular testing, and immunotherapy.
6. **Need for Improved Consistency:** Some diagnostic criteria, staging thresholds, terminology, tables, and reference citations require correction and standardization to improve scientific accuracy and readability.

Future Directions

Future research in multiple myeloma should focus on developing more effective and durable treatment strategies through precision medicine, comprehensive genomic profiling, and improved risk-adapted therapeutic approaches. Further studies are needed to establish the optimal role of measurable residual disease (MRD)-guided treatment decisions, including treatment

duration and the safe discontinuation of maintenance therapy in selected patients.

Advances in CAR T-cell therapy, bispecific antibodies, and other immune-based treatments may improve outcomes in patients with relapsed or refractory disease. Research should also address mechanisms of treatment resistance, antigen escape, relapse prevention, and the management of treatment-related toxicities. Prospective clinical trials and long-term follow-up studies are required to evaluate survival benefits, quality of life, cost-effectiveness, and real-world outcomes. Improving access to diagnostic testing and novel therapies, particularly in resource-limited settings, should remain an important priority.

CONCLUSION

The management of MM has moved from treatment based mainly on clinical disease burden to an approach that also considers cytogenetic risk, transplant eligibility, prior treatment, and depth of response. Proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, CAR T-cell therapies, and bispecific antibodies have broadened the treatment options described in this review. Despite these advances, relapse and treatment resistance remain important problems. Current clinical decisions therefore require individualized assessment and reference to up-to-date guidance, particularly as the evidence for newer therapies continues to evolve.

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Abbreviations:

- ASCT, autologous stem cell transplantation;
- MGUS,monoclonal gammopathy of undetermined significance
- FISH, fluorescent in situ hybridization;
- MM, multiple myeloma;
- OS, overall survival;
- SMM, Smoldering multiple myeloma;
- TTP, time to progression.
- LDH, lactate dehydrogenase;
- ISS, International Staging System.
- M, monoclonal;
- MRI, magnetic resonance imaging;
- PET-CT, positron emission tomography-computed tomography;
- FLC, free light chain
- SPEP, Serum Protein electrophoresis
- CR, Complete response

- MRD, Minimal Residual disease
- mAb, monoclonal antibody

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