Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

Differential Diagnosis and Therapeutic Advances in Multiple Myeloma: A Review Article

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Abstract: Multiple myeloma (MM) is a hematologic malignancy characterized by the abnormal clonal proliferation of plasma cells that may result in focal bone lesions, renal failure, anemia, and/or hypercalcemia. Recently, the diagnosis and treatment of MM have evolved due to a better understanding of disease pathophysiology, improved risk stratification, and new treatments. The incorporation of new drugs, including proteasome inhibitors, immunomodulatory drugs, anti-CD38 antibodies and high-dose chemotherapy followed by hematopoietic stem cell transplantation, has resulted in a significant improvement in patient outcomes and QoL. In this review, we summarize differential diagnoses and therapeutic advances in MM.

Keywords: multiple myeloma, myeloma, smoldering myeloma, Waldenstrom macroglobulinemia, light-chain amyloidosis

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the abnormal clonal proliferation of plasma cells in the bone marrow with a subsequent increase in the production of immunoglobulins. Abnormal production of immunoglobulins leads to organ damage characterized by anemia, hypercalcemia, focal bone lesions, and/or renal impairment. Based on these outcomes, the differential diagnosis of MM is broad (Table 1). Differential diagnosis includes monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), Waldenström Macroglobulinemia (WM), Light-Chain (AL) Amyloidosis, and plasmacytoma. Thus, prompt diagnosis of MM is essential because timely treatment significantly impacts outcomes and patient quality of life (QoL).

MM is the second most common hematologic malignancy, with an estimated incidence of 34,470 adults (19,100 men and 15,370 women) in the US in 2022.[5] MM is more common in Black compared to non-Hispanic White individuals and more common in men than women. The median age of initial diagnosis is 66 years.[6,7]

MM evolves from MGUS, a premalignant asymptomatic condition, which occurs in 3% of those over the age of 50.[8,9] MGUS progresses to MM or related malignancies, including AL amyloidosis, lymphoma, or WM, at a rate of 1% per year.[10] An intermediate, asymptomatic premalignant condition referred to as SMM carries a risk of progressing to MM of 10% per year in the first 5 years from initial diagnosis.[10] A recent study of >75,000 individuals—the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study—showed that SMM had a prevalence of 0.5% in individuals over 40 years old, was more common in men (0.7%) than women (0.4%) and an incremental incidence with age.[11] In most clinical cohorts of SMM, the median age of diagnosis is 65 years and is more common in Black individuals.

The introduction of newer therapies—immunomodulatory drugs, proteasome inhibitors (PIs), anti-CD38 antibodies, high-dose chemotherapy followed by hematopoietic stem cell transplantation, bispecific antibodies, and chimeric antigen T-cell therapy—has significantly improved progression-free survival (PFS) and/or overall survival (OS) in MM patients. In this review article, we will review the differential diagnosis of MM and treatment advances.

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Table 1 Differential Diagnosis of MM

Disease	Incidence	Blood Findings	Bone Marrow Examination	Clinical Manifestation
MGUS[1]	1–2% of adults older than 50 years	M protein level< 3g/dl	<10% plasma cells	Absence of myeloma-defining conditions or myeloma-related organ or tissue damage
Smoldering (Asymptomatic MM)	5 to 7 in 1,000,000	M protein level≥3 g/dl	10 to 59% plasma cells on bone marrow biopsy	Absence of myeloma-defining conditions or myeloma-related organ or tissue damage Definition of smoldering multiple myeloma include serum monoclonal protein (IgG or IgA) ≥3 g/dl or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 59% with absence of myeloma defining events or amyloidosis
Symptomatic MM	5 to 7 in 1,000,000	M protein level≥3 g/dl	≥60% plasma cells on bone marrow biopsy	Presence of at least one myeloma-defining condition or myeloma-related organ or tissue damage Myeloma-related organ damage includes. • Hypercalcemia (Calcium >1 mg/dl upper limit of normal or >11 mg/dl) • Kidney injury creatinine >2 mg/dl or Creatinine clearance <40 mL/min per 1.73 m2 • Anemia hemoglobin < 10 g/dl or >2 g/dl below lower normal limits • 1 ≥ lytic lesion on imaging studies Myeloma defining condition • Plasma cells ≥60% on bone marrow biopsy • Ratio of involved-to-uninvolved serum light chain is ≥100 or involved protein level ≥10 mg/dl or higher • >1 lytic lesion ≥5 mm on MRI[2] Definition of multiple myeloma include clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the Myeloma-related organ damage
Waldenström macroglobulinemia	7 to 10 per 1,000,000	IgM paraprotein	Hypercellular bone marrow with plasma cells, lymphocytes, and lymphoplasmacytic	Vision changes, Epistaxis, retinal changes, and Neurological changes. • Monoclonal gammopathy of an IgM should be present in serum irrespective of size.[3] • Bone marrow biopsy must demonstrate infiltration ≥10% by small lymphocytes that show plasmacytoid or plasma cell differentiation with intertrabecular pattern.[4] • Immunophenotype of infiltrates should be (IgM+, CD5-/+, CD10-, CD11c-, CD19+, CD20+, CD22+, CD23-, CD25+, CD27+, FMC7+, CD103-, CD138-) with plasmacytic component CD138+, CD38+ and CD45- or dim
Light-chain (AL) Amyloidosis	5 to 13 per 1,000,000	Immunoglobulin light chain	<10% plasma cells, Congo red staining on bone marrow biopsy or fat pad biopsy	Peripheral Neuropathy, Gastrointestinal symptoms, congestive heart failure
Plasmacytoma	Rare	N/A	Tumor positive for plasma cells, but bone marrow is negative for plasma cell neoplasms	Depending on up location Bone pain or compressive symptoms

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; MRI, Magnetic resonance imaging.

Monoclonal Gammopathy of Undetermined Significance

MGUS is a premalignant, asymptomatic plasma cell disorder and a precursor of MM, WM, and AL amyloidosis.[12] In 1960, Jan Waldenström described MGUS as "essential hyperglobulinemia" or "benign monoclonal gammopathy."[13] In 1978, Robert Kyle introduced the current term "monoclonal gammopathy of undetermined significance", based on a retrospective study of 241 patients with MGUS, of which a few progressed to MM, WM, or AL amyloidosis.[14] MGUS is defined by <10% clonal plasma cells in the bone marrow, the presence of serum or urine M (monoclonal) protein, and the absence of diagnosis of MM or other plasma cell dyscrasias and no evidence of any organ dysfunction attributable to the monoclonal protein.[2] Three different types of MGUS are recognized based on M-protein type: immunoglobulin M (IgM), non-IgM (IgG, IgA, or IgD), and light-chain MGUS. The risk of progression into a lymphoproliferative disorder differs for each subtype of MGUS.[15]

The prevalence of MGUS increases with age. It is observed in <0.3% of the population aged <40 years old, 3% of the population ≥50 years old, and 5% of the population ≥70 years old.[10,16] The incidence and prevalence are higher in Black than White individuals and higher in men than women.[17]

According to the 2014 International Myeloma Working Group (IMWG), MGUS is diagnosed when the following 3 criteria are met: serum M protein <3 g/dL or presence of abnormal free light-chain (FLC) ratio, bone marrow plasma cells <10%, and absence of end-organ damage due to plasma cells.[2]

The risk of progression of MGUS is associated with several factors,[18] the most important of which is an M protein spike of ≥15 g/L. Other risk factors include an IgA isotype, an abnormal free light-chain ratio of involved-to-uninvolved light chain ≥10, an increase in the M-protein level over time, bone marrow plasma cells >5%, a reduced level of uninvolved isotypes, and the presence of circulating plasma cells in the blood.

A model with the following biomarkers: M-protein ≥15 g/L, non-IgG MGUS, and abnormal FLC ratio of <0.125 or >8 was developed. Based on these factors, the 20-year risk of progression was 5% for those with no markers, 21% for those with 1, 37% for those with 2, and 58% for those exhibiting all of the markers (Table 2).[19]

Smoldering Multiple Myeloma

Smoldering Multiple Myeloma (SMM) is an intermediate condition between MGUS and MM. It is defined as an asymptomatic state where monoclonal protein ≥3 g/dL and/or 10–59% atypical plasma cells are present in the bone marrow, and there is no presence of end-organ damage (hypercalcemia, renal impairment, lytic lesions, or anemia) or other condition like amyloidosis or SLiM (60% or greater plasma cells in bone marrow, light-chain involvement with an involved-to-uninvolved ratio >100, and >1 focal lesion detected by magnetic resonance imaging [MRI]).[20] The understanding of SMM is evolving. The risk of SMM progressing to MM is variable and is estimated to be 10% per year in the first 5 years following diagnosis, 3% in the next 5 years, and 1.5% thereafter.[2] The median age of SMM onset is 67 years, with a high prevalence among Black individuals.[21] Black individuals have a lower risk of progression to MM in both univariate (HR 0.57, cl 0.34–0.94) and multivariate models (HR 0.39, Cl 0.16–0.95) compared to White individuals.[22] One-third of SMM patients never progress to MM.[23] According to the iStopMM study, the prevalence of SMM in the general population is 0.5%. The iStopMM study collected blood samples from 75,422 patients, followed by bone marrow sampling in 1562. SMM prevalence increases with age and is more common in males than females.[11]

There are several risk stratification models that assess the risk of SMM progression to MM, including the Mayo Clinic 2018 (20/20/2) model, IMWG criteria, and PETHEMA (Programa de Estudio y Tratamiento de las Hemopatias Maligna)

Table 2 Risk Stratification of MGUS-Based Mayo Clinic Risk Models

Risk Factors	Risk Category	% of Patients	Risk of Progression at 20 Years After Diagnosis
Serum M-protein <15 gm/l, IgG subtype and FLC ratio 0.26–1.65	Low risk	39	5
Any one factor	Intermediate risk	37	21
Any two abnormal factors	High intermediate risk	20	37
All three abnormal factors	High risk	5	58

Note: Data from Rajkumar et al.[19]

criteria, as shown (Table 3). It is important to note that there is variability of the results of those risk stratification models and none of them are perfect. The Mayo clinic 2018[24] model includes:

- Plasma cells >20%
- Free light-chain ratio >20
- Monoclonal protein M >2 g/dl

Table 3 Various Risk Stratification Models of Smoldering Multiple Myeloma Progression

Risk Stratification Models of Smoldering Multiple Myeloma	
Mayo 20/20/2 Score Model	
Risk factors	**Score**
Bone marrow plasma cells >20%	1
M-protein> 2 g/dl	1
FLC ratio >20	1
Risk category	**Progression Risk**
0 - Low	10% at 2 years 23% at 5 years
1 - Intermediate	26% at 2 years 47% at 5 years
>2 - High	47% at 2 years 82% at 5 years
IMWG score model	
Risk factors	**Score**
FLC ratio (involved to uninvolved)	
0–10	0
>10–25	2
>25–40	3
>40	5
M-protein level (g/dl)	
0–1.5	0
>1.5–3	3
>3	4
Bone marrow plasma cells in %	
0–15	0
>15–20	2
>20–30	3
>30–40	5
>40	6

(*Continued*)

Table 3 (Continued).

Risk Stratification Models of Smoldering Multiple Myeloma	
FISH t (4;14), t (14;16), +1q, del 13q, monosomy 13	2
Risk category	**Progression Risk**
0–4 – Low	4% at 2 years 20% at 5 years
5–8 – Low-intermediate	26% at 2 years 55% at 5 years
9–12 Intermediate	51% at 2 years 70% at 5 years
>12 – High	73% at 2 years 85% at 5 years
PETHEMA score model	
Risk factors	**Score**
≥95% aberrant plasma cells in bone marrow by multiparameter flow cytometry	1
Presence of immunoparesis	1
Risk category (score)	**Median TTP**
0	NR
1	73 months
2	23 months

Per the Mayo Clinic 2018 model, high-risk SMM includes 2–3 of the above factors with an estimated median time to progression of 29 months. The estimated risk of high-risk SMM progression to MM is 24% per year in the first 2 years, 11% per year within the next 3 years, and 5% in the next 5 years. The model defines intermediate-risk SMM as having one factor and estimates the time to progression to MM as 68 months. The estimated risk of intermediate-risk SMM progression to MM is 15% per year during the first 2 years, 7% per year during the next 3 years, and 4% per year for the next 5 years. Low-risk SMM is defined as having no factors present, and the estimated time to progression is 110 months. The estimated rate of low-risk SMM progression to MM is 5% per year during the first 10 years. IMWG validated Mayo Clinic's risk stratification model in 1996 patients and found a 2-year risk of progression to MM or amyloidosis of 6% in low-, 18% in intermediate-, and 44% in high-risk SMM groups.[25]

The PETHEMA model includes immunoparesis and the percentage of plasma cells with aberrant immunophenotype, but the multiparameter flow cytometry requirement of the PETHEMA model makes it more difficult to implement clinically.[26]

Observation continues to be the most appropriate strategy for SMM management, regardless of risk stratification. This strategy is supported by the high incidence of SMM in large population studies and the lack of improvement in OS and/or QoL with earlier SMM treatment, and it is our recommended strategy at the University of Arkansas for Medical Sciences for all patients with SMM regardless of risk stratification.

Two treatment strategies were evaluated for high-risk SMM: control (low-intensity therapy aiming to delay time to organ damage) vs intensive chemotherapy to eradicate and potentially cure the disease.[27]

The QuiRedex Phase 3 multicenter trial studied a population of 119 patients with SMM[28] and assigned 57 patients to a lenalidomide and dexamethasone treatment group and 62 to an observation-only group. The median follow-up was 75 months. The treatment arm showed a longer time of SMM progression to active MM compared with the observation group (median time to progression not reached [95% CI 47 months-not reached] vs 23 months [16–31]; hazard ratio 0.24

[95% CL 0.14–0.41]; p < 0.0001). In the observation group, 86% (53/62) of the patients progressed to MM compared to 39% (22/57) in the treatment group. The most important criticism of this study was that modern imaging techniques like MRI and whole-body positron emission tomography CT (PET-CT) were not used. It was also a possibility that a few MM patients were enrolled as SMM patients.

Another randomized phase 3 clinical trial[29] in a population of 182 intermediate- or high-risk SMM patients assigned 92 patients to a lenalidomide treatment group and 90 to an observation-only group. Lenalidomide was administered on days 1 through 21 of a 28-day cycle. The primary endpoint was PFS, biochemical progression, and development of end-organ damage due to MM. The median follow-up was 35 months. PFS was longer in the lenalidomide treatment group compared to the observation-only group (hazard ratio 0.28; 95% Cl 0.12 to 0.62; p = 0.002). One-, two- and three-year progression-free survival was 98%,93%, and 91% for the lenalidomide arm vs 89%,76%, and 66% for the observation arm, respectively. Six deaths were reported, two in the lenalidomide arm vs four in the observation arm (hazard ratio for death, 0.46; 95% Cl, 0.08 to 2.53). This study had certain limitations. Initially, patients diagnosed in the previous year were enrolled in the study, but due to low recruitment, the protocol was altered to allow enrollment of patients diagnosed in the previous 5 years. It is possible that SMM patients that failed to progress to MM did not have high-risk SMM. Forty-seven percent of the patients had abnormal MRI at baseline, raising concerns for active MM as PET-CT was not a study requirement. In the observation arm, 24% of patients progressed to MM by 24 months, which was less than the anticipated 50%, suggesting a poor representation of high-risk SMM cases. According to the 2018 Mayo Clinic criteria, 58 patients were low risk. These criteria also identified 29 high-risk patients, of which 14 were assigned to the treatment arm. Due to an underpowered population, PFS statistics were not applied, and there were missing data on fluorescence in situ hybridization (FISH) genetics in 102/182 patients. This study included a QoL assessment with no significant difference in mean change score at 24 months. The low rate of progression and side effect concern makes it difficult to use this study in clinical practice.[27]

In the GEM-CESAR[30] Phase 2, single-arm clinical trial of 90 patients with high-risk SMM or asymptomatic MM (based on 1 of 3 new biomarkers), 78 received KRD (carfilzomib, lenalidomide, dexamethasone) followed by autologous stem cell transplantation (ASCT) and KRD consolidation and maintenance for 2 years. At 30 months of follow-up, the overall response rate (ORR) was 100%, and complete response (CR) was 76%, with a minimal residual disease (MRD) rate of 63%. Three out of 90 patients died, four patients withdrew, and eight patients progressed from MRD negative to MRD positive. Thirty-one patients (34%) had at least one of the biomarkers considered myeloma-defining events that are currently classified as active MM. Grade 3–4 neutropenia and thrombocytopenia were reported in five (6%) and ten (18%) patients, respectively. Infection was observed in 16 patients (18%), and 8 (9%) patients had skin rash. Seven patients had to discontinue the maintenance regimen due to several complications, including cardiac arrest in one patient, four patients had hematological toxicity, and two patients had secondary malignancies.

In the ASCENT phase 2 clinical trial,[31] 46 SMM high-risk patients (70% male) with a median age of 63 years (range 47–76) were enrolled. Patients received 6 cycles of induction therapy with daratumumab (weekly for 8 weeks, then every other week for 16 weeks) and KRD (carfilzomib twice weekly, lenalidomide 25 mg daily for 3 weeks, dexamethasone 40 mg weekly) but in consolidation daratumumab every 4 weeks and dexamethasone 20 mg weekly. Patients received 12 cycles of maintenance with lenalidomide 10 mg daily for 3 weeks and daratumumab on day 1 every other cycle of a 4-week cycle. This study is still ongoing, but safety data showed concerning grade 3–4 adverse events, including cytopenia, infections, hypertension, diarrhea, and allergic reactions in less than 10% of patients, and 52% had at least one grade >2 adverse event. Given the asymptomatic nature of SMM and evolving definitions, high intensity treatments that do not improve OS and/or QoL while increase risk of serious adverse events should be discouraged unless planned in a clinical trial setting with an observational control arm.

Multiple Myeloma

MM is a hematological malignancy characterized by uncontrolled proliferation of plasma cells causing bone destruction, anemia, hypercalcemia, and/or acute kidney injury.[32] There is no known etiology of MM, but risk factors are male sex, obesity, occupation (eg, firefighter), and dioxin and Agent Orange exposure.[33] In newly diagnosed MM, typical findings include anemia (hemoglobin <12), one or more lytic lesions on a conventional radiograph in 79% of cases, elevated

creatinine in 19% of cases, lymphadenopathy in 1% of cases, hypercalcemia in 13% of cases, and thrombocytopenia in 5% of cases.[7] In newly diagnosed patients, 3.3% had extramedullary disease (presence of 1 or more extraosseous plasmacytomas on cross-sectional imaging), central nervous system involvement, and plasma cell leukemia. Extramedullary disease is aggressive both in newly diagnosed and relapsed refractory multiple myeloma (RRMM).[34] About 10–15% of patients with MM are diagnosed with concurrent immunoglobulin light-chain amyloidosis during the course of the disease.[35]

Diagnostic evaluation of MM includes a complete blood count, imaging, urine studies, and bone marrow biopsy (Table 1). Blood tests included blood count with differential, serum creatinine, calcium level, albumin, lactate dehydrogenase, free serum light-chain level, beta-2 microglobulin levels, and serum protein electrophoresis with immunofixation. Serum protein electrophoresis shows monoclonal protein in 86% of patients.[7] Urine tests include 24-hour urine collection to quantify Bence-Jones protein for baseline proteinuria, as secondary light-chain amyloidosis can have nephrotic range proteinuria. About 1–2% of all MM patients have nonsecretory MM, defined by no measurable serum or urine markers.[36] In newly suspected MM, every patient should have a bone marrow biopsy, flow cytometry, cytogenetics, and FISH. Imaging includes MRI, PET-CT, whole-body low-dose CT, or bone survey in the absence of an advanced imaging modality.[33] Revised IMWG diagnostic criteria for MM include 10% or greater plasma cells in the bone marrow and at least one type of end-organ damage (hypercalcemia, renal disease, anemia, and/or bone lytic lesion) or a myeloma defining SLiM criteria event (plasma cells >60% in bone marrow, free light-chain involved-to-uninvolved ratio >100, and more than one focal lesion on MRI) (Table 1).[37]

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by an elevated level of immunoglobulin M (IgM).[38] It is a rare disorder, with 1400 new cases in the US and an overall incidence of 3 per million persons per year.[39,40] It is more prevalent in White men and has a median age of diagnosis of 70 years.[41,42] Clinical features are due to infiltration of IgM and include anemia, peripheral neuropathy, lymphadenopathy, and hepatosplenomegaly.[43] A study of 217 patients diagnosed with WM showed the following features.[44]

- Fundoscopic findings in 34% were characterized by dilated tortuous, segmented, sausage-shaped veins with hyperviscosity. Other findings include papilledema, hemorrhages, and papilledema, so patients with IgM levels >3000 mg/dL with hyperviscosity-related symptoms should have a fundoscopic examination.
- Bleeding in 23% of the patients, mainly due to hyperviscosity. Hyperviscosity causes platelet and clotting factor dysfunction.
- Constitutional "B" symptoms (fatigue, generalized weakness, weight loss, night sweats, and oronasal bleeding) in 23% of the patients.[45]
- Symptoms related to hyperviscosity in 31% of the patients included headache, vertigo, nystagmus, dizziness, blurring or loss of vision, deafness, or ataxia. Patients can have confusion, dementia, stroke, or coma in severe cases. Hyperviscosity can also precipitate or exacerbate congestive heart failure.[44,46–48]
- Neurological symptoms in 22% of the patients at the time of diagnosis, the most common being distal, symmetric, progressive sensorimotor neuropathy leading to generalized sensory loss and paresthesia.[49,50]
- Lymphadenopathy in 25% of patients and hepatomegaly in 24% of patients. Splenomegaly is often observed in newly diagnosed WM patients, and they can present with spontaneous spleen rupture.[51]

Diagnosis of WM is based on clinical presentation, bone marrow biopsy, and analysis of serum protein electrophoresis.[4,52] For diagnosis of WM, criteria must be met, as shown in Table 1. Monoclonal gammopathy of an IgM should be present in serum, irrespective of level.[3] Bone marrow biopsy must demonstrate small lymphocyte infiltration ≥10% that shows plasmacytoid or plasma cell differentiation with an intertrabecular pattern.[4] Ninety percent of WM patients may have MYD88, L265P, and/or CXCR4 gene mutations, which are helpful in differentiating from other conditions for therapy selection and are prognostic.[53,54]

Light-Chain Amyloidosis

Light-chain (AL) amyloidosis is a multisystem disease caused by the deposition of fibrillary protein, producing dysfunction of affected organs.[55] Because amyloidosis is nonspecific and has variable presentation, it is difficult to assess how many people are affected, and diagnosis is usually missed and delayed. About 4000 people are diagnosed with amyloid and AL amyloidosis every year in the US, with a median age between 50 and 65 years.[56] The incidence of amyloidosis ranges from 9.4 to 14.0 cases per 1 million persons.[57] Clinical features depend upon the type of protein and the extent and pattern of involvement.[58] Systemic amyloidosis is due to the formation of insoluble amyloid fibrils that are due to the deposition of misfolded proteins. These proteins number over 30.[59] AL amyloidosis is due to the deposition of a monoclonal light chain and can be associated with monoclonal gammopathy, MM, and B-cell lymphoma. AL amyloidosis has direct cardiotoxic, cytotoxic, and proapoptotic effects.[60]

ATTR amyloidosis is due to the deposition of transthyretin protein. Transthyretin is a protein produced by the liver, and its main function is the transportation of thyroid hormone and vitamin A.[61] ATTR amyloidosis can be further differentiated into wild type (wtATTR) and hereditary subtypes (mutated vATTR).[55] It is important to characterize the type of amyloid by mass spectrometry for all patients with amyloid deposition.

Amyloidosis predominantly involves the heart, kidney, liver, and gastrointestinal tract, but the lung, nervous system, muscles, and soft tissues can also be affected. These effects vary by subtype, with the vATTR subtype mainly affecting the heart and AL having more systemic involvement.[62] Cardiac manifestation includes heart failure with preserved ejection fraction, exertional dyspnea, hypotension, angina, and cardiac arrhythmia. Renal involvement includes non-selective proteinuria or renal failure.[63] Neuropathic effects involve both the somatic and autonomic systems and cause the loss of temperature and pain sensation, as well as numbness and weakness that lead to imbalance. Autonomic manifestations include altered bowel habits, orthostatic hypotension, urinary retention, and erectile dysfunction.[64] Gastrointestinal tract symptoms include weight loss due to malabsorption, ulcers, perforation, and bowel dysmotility. Liver effects include hepatomegaly, hyposplenism, and liver failure.[65] Patient can also present with muscle weakness, carpal tunnel syndrome, lumbar spinal stenosis, and alopecia.[62]

Therapeutic Advances in Multiple Myeloma

Due to the results of several clinical trials, MM treatment has been drastically changed both in newly diagnosed MM and RRMM settings. The introduction of novel treatments has changed OS, PFS, and QoL with less toxicity.[66] The introduction of anti-CD38 monoclonal antibodies has revolutionized MM treatment across all settings and has now been followed by treatment with chimeric antigen receptor T (CAR-T) cells and bispecific antibodies both of which are showing early promising results. These drugs may become superior to conventional therapy due to their favorable toxicity profiles and high efficacy. New immune-based drugs with varying mechanisms of action, such as antibody-drug conjugates, immunomodulators, cereblon E3 ligase modulators, and fusion proteins are currently in development. Commonly used therapeutic agents are summarized in Table 4.

Newly diagnosed MM patients are treated with induction combination therapy. This treatment is usually at least a triple combination such as lenalidomide, dexamethasone, and bortezomib or different regimens depending upon the eligibility of patients for autologous stem cell transplant (ASCT).[67] The main objective of the first phase of treatment is the reduction in tumor burden and better collection of stem cells.[68] Melphalan-based regimens are no longer the standard of care in induction chemotherapy as they interfere with stem cell collection.[69] After induction chemotherapy, patients are administered high-dose melphalan followed by ASCT.[70] After ASCT, the patient will be treated with consolidation and/or maintenance/extended therapy based on various factors.[71] For RRMM, there are several new treatment options, including novel combinations.[71]

Alkylating Agents

Alkylating agents have long been used in the treatment of MM. Those most commonly used are melphalan and cyclophosphamide. Alkylating agents work by breaking the double strand of DNA, leading to apoptosis.[72] Melphalan was the first alkylating agent and the standard of care, in combination with prednisone, in 1961.[72] In the last two decades, melphalan use has generally decreased with the development of novel agents; however, it is still used at a high dosage as

Table 4 Overview of Various Therapeutic Agents for Treatment of MM

Class	Target	Relevant Consideration	Effects on MM
Proteasome inhibitor (PI)			
• Bortezomib • Carfilzomib • Ixazomib	Proteasome	• Peripheral Neuropathy • Risk of Herpes zoster • Dose adjustment in hepatic dysfunction • Heart failure • Hypertension • Renal failure	• Bortezomib stimulates osteoblast differentiation and inhibits osteoclast activation induced by RANKL. • PI inhibits auto and paracrine signaling in MSCs. Pls decrease MM cell adhesion to BMSCs
Immunomodulator drugs (IMiD)			
• Thalidomide • Lenalidomide • Pomalidomide	CRBN	• VTE prophylaxis • Can interfere with stem cell mobilization. • Risk of secondary malignancies • Dose adjustment in renal dysfunction	• T-cell co-stimulatory effects • Anti-angiogenesis • Anti-inflammatory effects • Promotes anti-proliferative effects
Monoclonal antibodies			
• Daratumumab • Isatuximab • Elotuzumab	Daratumumab and Isatuximab acts as anti-CD38 Elotuzumab acts via SLAMF7.	• Acute or delayed infusion reaction • Herpes zoster and opportunistic infection • Interfere with SPEP and Immunofixation • It can interfere with crossing matching and antibody screening	• Increases helper and cytotoxic T cell counts and memory T cells. • Augment NK cell cytotoxicity • Destroys CD+38 immune suppressor cells like Tregs and Bregs **Elotuzumab** • Causes TAM activation • Mediates ADCP **Isatuximab** • Destruction of C38+ immunosuppressive cells like Tregs
Alkylating agents			
• Melphalan • Cyclophosphamide	DNA fragmentation and damage	• Myelosuppression • Alopecia • Mucositis	
Nuclear export inhibitor			
Selinexor	Exportin 1	• GI toxicity • Hyponatremia • Neurological symptoms	• Enhanced NK cell cytotoxicity and ADCC • Decreases pro-survival signals from the bone marrow microenvironment
BiTE therapy			
• Teclistamab • Talquetamab	**Teclistamab** BCMA X CD3 **Talquetamab** GPRC5D X CD3	• CRS • Neurotoxicity • Serious infection • Hepatoxicity	**Teclistamab** Bridging between myeloma cells and T cells causing cell death. **Talquetamab** Actively kills GPRC5 D positive myeloma cells.

(*Continued*)

Table 4 (Continued).

Class	Target	Relevant Consideration	Effects on MM
CAR-T cell therapy			
• Idecabtagene Vicleucel	TNFRSF 17 (BCMA)	• CRS • Neurotoxicity • Pancytopenia • Prolonged hypogammaglobinemia	T cells are recruited and linked to antigen on myeloma cells and decrease BM induced immunosuppression.
• Ciltacabtagene autoleucel	TNFRSF 17 (BCMA)		Reduces BCMA cell expression and BM induced immunosuppression
Corticosteroids			
Dexamethasone Prednisone	Glucose response element (NF-kB)	• Hyperglycemia • Insomnia • Fluid retention	Induces apoptosis of MM cells
Venetoclax	T (11, 14)	• Infection • Bladder pain	Restores process of apoptosis

Abbreviations: RANKL, Transmembrane molecule expressed by mesenchymal cell and lymphocyte; VTE, Venous thromboembolic; SLAMF7, Signaling lymphocytic activation molecule 7; SPEP, serum protein electrophoresis; TAM, Targeting Tyro3 Axl and Mer TK; ADCP, Antibody dependent cellular phagocytosis; GI, Gastrointestinal; CRS, Cytokine releasing syndrome; BM, Bone marrow; BCMA, B-cell maturation antigen; NF-Kb, nuclear factor kappa light-chain enhancer of activated B cells.

a conditioning regimen before ASCT, and it is also used in combination with dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide, and etoposide in aggressive disease.[73]

Cyclophosphamide, another commonly used alkylating agent, has strong immunomodulatory effects through the activation of natural killer cells, macrophages, and helper T cells and is currently used in combination with other standards of care.[72] Another alkylating agent, melflufen, causes irreversible damage to DNA and produces apoptosis through a P53-independent mechanism. Melflufen is no longer used due to inferior outcomes compared to other drug therapies.[74]

Proteasome Inhibitors

Proteasome inhibitors (PIs) are one of the most important therapeutic agents in MM management. Proteasome is a large protease complex that causes the degradation of proteins in the nucleus and cytoplasm. In MM cells, several proteins are produced. Inhibiting proteasome causes these proteins to accumulate in the cytoplasm and endoplasmic reticulum, causing what is called endoplasmic reticulum stress and inducing apoptosis and the destruction of MM cells.[75] In addition to apoptosis, PIs inhibit angiogenesis and cell cycle arrest, as shown in Figure 1.

Bortezomib was the first PI to gain FDA approval in 2003. Bortezomib is a boronic acid dipeptide that binds to the chymotrypsin and caspase and inhibits its activities, causing myeloma cell destruction.[76]

Carfilzomib and ixazomib are two next-generation PIs.[75] Carfilzomib, approved in 2012, irreversibly inhibits proteasome by binding to the β5 subunit.[77] It has different adverse effects compared to other PIs. The most concerning adverse effect is cardiotoxicity, which is due to the autophagy pathway and upregulation of protein phosphatase-2A activity and not due to proteasome inhibition.[78] Ixazomib is an oral and reversible PI. It binds to the β5 subunit of the 20S proteasome and inhibits its chymotrypsin-like activity. Its half-life is short compared to other PIs,[79] as shown in Figure 1. Ixazomib should not be used in maintenance setting in the context of modern therapy given inferior outcomes, and its use in general in treating MM is not recommended in our practice.

Corticosteroids

Steroids are the backbone of MM treatment, both for newly diagnosed MM and RRMM. In modern treatment regimens, steroids are combined with novel agents to increase the depth of clinical response. Glucocorticoids induce apoptosis in MM cells either by transactivation of glucocorticoid response elements, phosphorylation of RAFTK (Pyk2), or transrepression of NF-Kappa B, but its exact mechanism of action is still unknown.[80]

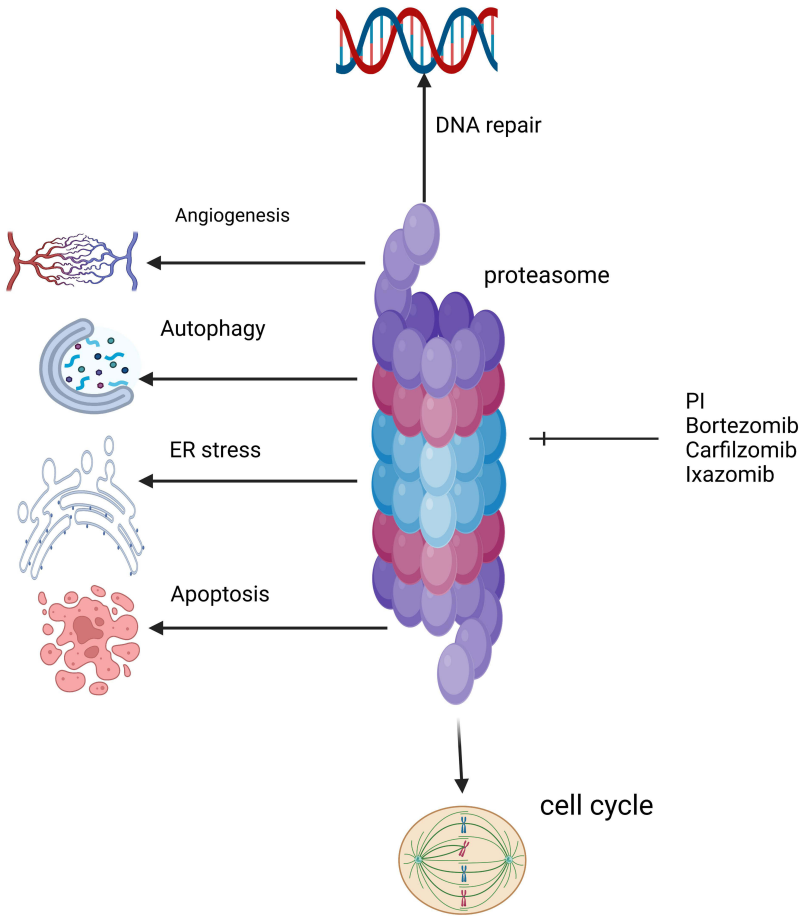

Figure 1 Mechanism of proteasome inhibitor action on multiple myeloma cells.

The Eastern Cooperative Oncology Group (ECOG) pilot study[81] assessed the efficacy and safety of dexamethasone in 32 patients with advanced MM, of which 26 had received several lines of prior treatment. Patients received 40 mg of oral dexamethasone 4 days per week for 8 weeks. Those patients who responded to treatment were maintained on the same treatment administered at a 2-week interval. On analysis, 13/32 (40%) patients responded based on ECOG criteria. Moderate-to-severe side effects were observed in 9 patients (55%), including 9 with central nervous system effects, 3 with gastrointestinal bleeding, 2 with pulmonary emboli, and 1 with psychosis. Coadministration of corticosteroids with bortezomib has been shown to decrease the severity of peripheral neuropathy.[82]

Autologous Stem Cell Transplantation

ASCT (single and tandem) is a consolidation therapy in transplant-eligible, newly diagnosed MM patients with no age cut-off in the US.[83] The first melphalan-based ASCT treatment of 9 patients was performed successfully in 1983.[84] Barlogie et al showed that melphalan-induced myelosuppression could effectively be rescued with ASCT.[85] Wildes et al[86] showed prolonged median OS in older patients aged 65–77 years treated with ASCT compared to a non-ASCT group. Median OS was 56.0 months in the ASCT group (95% CI [49.1–65.4]) compared to 33.1 months in the non-ASCT group (24.3–43.1) ($p = 0.004$) with no increased mortality after adjusting for performance status, comorbidities, and disease status.

An open-label randomized phase 3 clinical trial[87] compared melphalan-prednisone-lenalidomide (MPR) treatment to treatment with ASCT followed by lenalidomide and dexamethasone. Both PFS and OS were longer in the ASCT group when compared to the MPR group (4-year OS 81.6% vs 65.3%, $p = 0.02$; median PFS 43.0 months vs 22.4 months).

Cavo et al[88] conducted a randomized phase 3 clinical trial that showed that bortezomib-based induction therapy followed by ASCT had improved PFS compared to VMP alone (Table 5).

Table 5 Various Phase III Clinical Trials Showed Improved Outcomes with Autologous Stem Cell Transplantation

Clinical Trials/ Study	Patients	Intervention	PFS	OS
Palumbo et al[87]	Total 273 ASCT group=141 Non-ASCT=132	RD 4 cycles followed by ASCT vs MPR 6 cycles Followed by maintenance with ±R	Median PFS 43 months vs 22.4 months p<0.001	4-year OS 81.6% vs 65.3% p=0.02
Cavo et al[88]	Total 1192 ASCT group=695 Non-ASCT=497	Induction therapy with bortezomib based regimen followed by ASCT vs VMP+VRD x 4 and maintenance with R	3-year PFS 64% vs 57% p=0.002	3-year OS: 85% in both groups
Attal et al[89]	Total 700 ASCT group=350 Non-ASCT=350	VRD 3 cycles followed ASCT vs VRD 5 cycles +Maintenance with R	Median PFS 50 months vs 36 months p<0.001	4-year OS 81% vs 82% p=0.87
Gay et al[90]	Total 256 ASCT group=127 Non-ASCT=129	RD 4 cycles followed by ASCT vs RCD 6 cycles Followed by maintenance with R	Median PFS 43.3 months vs 28.6 p<0.0001	4-Years OS 86% vs 73% p=0.004

Abbreviations: ASCT, autologous stem cell transplantation; PFS, progression free survival; OS, overall survival, RD, Lenalidomide-dexamethasone; MPR, melphalan-prednisone-Lenalidomide; VMP, bortezomib-melphalan-prednisone; VRD, bortezomib-Lenalidomide-dexamethasone.

An open-label, large phase 3 trial by Attal et al[89] randomized patients into groups receiving either induction therapy with bortezomib, lenalidomide, and dexamethasone (VRD) followed by consolidation therapy with VRD or ASCT and followed by additional cycles of VRD. Both groups received lenalidomide maintenance therapy for up to 1 year. The median PFS and complete response were significantly longer in the ASCT group than in the non-transplant group (50 months vs 35 months; $p < 0.001$, 59% vs 0.48%, $p = 0.03$).

An open-label, phase 3 clinical trial by Gay et al randomized patients into groups receiving either chemotherapy plus lenalidomide or induction chemotherapy (Lenalidomide and dexamethasone) followed by ASCT. This trial showed improved PFS in the ASCT group compared to that in the other treatment group (median PFS 43.3 months vs 28.6 months, $p < 0.0001$),[90] as shown in Table 5.

Whether to perform ASCT early or to delay it is sometimes debated. It is our recommendation to proceed with upfront ASCT in patients who are eligible for it. A retrospective study[91] of 363 MM patients showed that ASCT performed <12 months after diagnosis improved PFS and demonstrated a higher response rate. The median age of patients was 52 years (range 20 to 72 years), and 233 (64.2%) were male. The median time from diagnosis to transplant was 11.5 months (range 4–67.5); 201 (55.4%) patients had ASCT within 12 months of diagnosis (early), and 162 (44.6%) patients had ASCT >12 months since diagnosis (delayed). Post ASCT analysis showed better CR (77.1% vs 64.8%, $p < 0.025$) and improved very good partial response (VGPR, 89% vs 81.5%, $p < 0.03$) in the early ASCT group compared to the delayed group. Transplant-related mortality at 100 days was similar among both groups. (3.5% vs 3.7%; $p = 0.564$) DETERMINATION trial[92] compared RVd plus melphalan-based ASCT to RVd alone. Median PFS was better in the transplant group 67.5 vs 46.2 months (HR 1.53; 95% CI, 1.23–1.91; $p < 0.0001$) with no difference in 5-year OS between both groups.

Immunomodulatory Drugs

Immunomodulatory drugs (IMiDs) include thalidomide, lenalidomide, and pomalidomide. IMiDs have pleiotropic effects on MM with the ability to modulate host immune response and angiogenesis, impact cytokine secretion and inflammation, and produce direct cytotoxic effects on MM, including growth arrest and caspase-8-mediated apoptosis.[93,94] These drugs represent a paradigm shift in the treatment of newly diagnosed MM and RRMM.[95] Thalidomide is a synthetic derivative of glutamic acid with two active enantiomers, S and R. The S enantiomer is responsible for antitumor effects, and the R enantiomer has sedative effects.[96] The combination of Bortezomib, Thalidomide, and dexamethasone (VTD) is a standard induction

chemotherapy regimen in transplant-eligible, newly diagnosed MM patients. Several clinical trials have shown the superior efficacy of VTD over other drug combinations used in pre-ASCT induction treatments.[97,98]

A phase 3 study by Cavo et al[97] compared VTD to the combination of thalidomide and dexamethasone as induction therapy before ASCT and showed CR or near complete response (nCR) of 33.1% vs 13.7% ($p < 0.0001$). Three-year PFS was longer in the VTD group (60% vs 48%, $p = 0.042$).

Another phase 3 trial[99] compared VTD to bortezomib, cyclophosphamide, and dexamethasone (VCD) as pre-ASCT induction therapy and showed overall response rates (ORR) of 92.3% vs 83.4% ($p = 0.01$), respectively. In addition, VTD showed a VGPR of 66.3% compared to 56.2% for VCD ($p = 0.05$).

Phase 3 PETHEMA/GEM 12 study[100] evaluated the efficacy and safety of VRD as an induction regimen. In this study 458 NDMM, patients aged <65 years received 6 cycles of VRD followed by ASCT with a conditioning regimen of busulfan and melphalan vs melphalan. The patient received consolidation with 2 cycles of VRD. In grouped response analysis of 6 induction cycles ($n = 426$), VGPR or better was achieved at 55.6% by cycle 3, 63.8% by cycle 4 and 68.3% by cycle 5, and 70.4% by cycle 6. About 33.4% had CR after induction in the intent-to-treat population (ITT) which was similar in the 92 patients with high-risk cytogenetics (34.8%). This response further deepened to 44.1% after ASCT and 50.2% after consolidation. In the ITT, the rate of undetected minimal residual disease (sensitivity 3×10^6) increased from induction (28.8%) to transplant (42.1%) and consolidation (45.2%). During induction, common adverse events grade 3 were neutropenia (12.9%) and infection (9.2%). Seventeen percent of patients had grade 2 peripheral neuropathy, 3.7% grade 3, and 0.2% grade 4 during induction. VRD is a well-tolerated and effective induction regimen in NDMM patients.

The CASSIOPEIA randomized phase 3 trial compared a quadruplet regimen of daratumumab and VTD to a triplet VTD regimen as induction therapy for ASCT eligible patients and showed a CR or better in 39% vs 26%, respectively ($P < 0.0001$).[101]

New IMiDs include iberdomide and mezigdomide (MEZI). Iberdomide is a cereblon E3 ligase modulator with stronger anti-tumor and enhanced immune stimulatory effects compared to other IMiDs. In Phase 1/2 trial,[102] iberdomide was studied with oral dexamethasone in a dose-escalation cohort and a dose-expansion cohort. The dose-escalation cohort contained individuals who had been administered at least 2 previous lines of therapy, including lenalidomide or pomalidomide and PIs. Patients received escalating doses of Iberdomide (0.3–1.6 mg on days 1–21 of each 28-day cycle) and oral dexamethasone (40 mg or 20 mg [if age ≥75 years]) once a week. The dose-expansion cohort contained patients with RRMM who had received at least 3 previous lines of therapy and had triple-class refractory disease (refractory to IMiDs, PIs, and CD38 antibodies). Patients were treated with the recommended phase 2 dose, and treatment continued until their disease progressed or unacceptable toxicity was observed. ORR was 32% (95% CI 23–43) across all doses in the dose-escalation cohort and 26% (95% CI 18–36) in the dose-expansion cohort, respectively. Overall, the most common grade 3 or worse adverse effects were neutropenia in 45% of the patients, anemia in 25%, infection in 27%, and thrombocytopenia in 22%. There was 1% treatment-related mortality, and 5% of the patients discontinued treatment due to intolerable toxicity.

MEZI is an oral cereblon E3 ligase modulator with strong antimyeloma activity that has shown strong synergy with dexamethasone, PIs, and anti-CD38 monoclonal antibodies in the treatment of RRMM.[103]

Bcl (a B-Cell Lymphoma-2) Inhibitor

Venetoclax is BCL-2 inhibitor able to reinstate the apoptotic potential of cancer cells. Patients with MM cells with translocation t (11; 14) have higher BCL-2 expression and can benefit from venetoclax-based therapy.[104]

The BELLINI trial (phase 3, randomized, double-blind, multicenter) demonstrated that combining venetoclax with dexamethasone and bortezomib improved median PFS in patients with RRMM who had received one to three prior therapies. Patients were randomly assigned to receive either venetoclax (800 mg orally daily) or placebo, both with bortezomib (1.3 mg/m2 subcutaneously or intravenously) and dexamethasone (20 mg orally). Median follow-up was 18.7 months. The independent review committee found a median PFS of 22.4 months (venetoclax group) vs 11.5 months (placebo group) with a hazard ratio of 0.63 ($p = 0.010$). The most common grade 3 or worse adverse events in the venetoclax group were neutropenia (18%), pneumonia (16%), thrombocytopenia (15%), diarrhea (15%), and anemia (15%), with 8 fatal infections noted in the venetoclax group. Nevertheless, the venetoclax group exhibited higher mortality, primarily attributed to a heightened infection rate, underscoring the significance of carefully selecting patients suitable for this therapeutic approach.

Monoclonal Antibodies

CD38 is a glycoprotein expressed on MM cells. Daratumumab is an anti-CD38 monoclonal antibody. Daratumumab works through several mechanisms, including antibody-dependent cellular toxicity, antibody-dependent cellular phagocytosis, complement-mediated cytotoxicity, direct apoptosis, and immunomodulation by depleting CD38 positive immune suppressive cells with the expansion of T effector cells.[105] Daratumumab is used in upfront in newly diagnosed MM as well as RRMM.

Isatuximab is another anti-CD38 monoclonal antibody with a different mechanism of action from daratumumab.[106] Isatuximab binds to a specific epitope on the human CD38 receptor. Like daratumumab, isatuximab can induce direct apoptosis and has demonstrated antitumor activity in xenograft models of MM, acute lymphoid leukemia, and non-Hodgkin's lymphoma.[107]

A phase 3 prospective randomized open-label trial (IKEMA)[108] compared the combination of isatuximab with carfilzomib-dexamethasone (isatuximab group) to carfilzomib-dexamethasone alone (control group) in RRMM patients. Median PFS was not reached in the isatuximab group, in contrast to 19.15 months (95% CI 15.77 to not reached) in the control group, yielding a hazard ratio of 0.53 (99% CI 0.32 to 0.89; one-sided p = 0.0007). Grade 3 or worse treatment-related adverse events (AEs) occurred in 136/177 (77%) of the isatuximab group and 82 (67%) of 122 in the control group. AEs leading to treatment discontinuation were observed in 15 (8%) vs 17 (14%) in the isatuximab vs control groups, respectively. The addition of isatuximab to carfilzomib-dexamethasone led to improved PFS and response depth in RRMM.

In the ICARIA trial, a randomized open-label multicenter phase 3 study,[109] isatuximab was compared to pomalidomide and dexamethasone (isatuximab group) in RRMM patients aged >18 years. Eligible patients had received at least two lines of therapy, including lenalidomide and PI. Patients refractory to anti-CD38 therapy or those who had received pomalidomide were excluded. Of the 307 patients, 154 were assigned to the isatuximab group and 153 to the control group. Median OS was 24.6 months (95% CI 20.3 to 31.3) in the isatuximab group and 17.7 months (14.4 to 26.2) in the control group, with a hazard ratio of 0.76 (95% CI 0.57 to 1.01). Grade 3 or worse treatment-related AEs included neutropenia (76 [50%] of 152 patients vs 52 [35%] of 149 patients) and other adverse events like pneumonia (35 [23%] vs 31 [21%]) and thrombocytopenia (20 [13%] vs 18 [12%]) in the isatuximab and control groups, respectively.

In the ALCYONE randomized trial,[108] newly diagnosed transplant-ineligible MM patients received nine cycles of bortezomib, melphalan, and prednisone alone (control group) or in combination with daratumumab until disease progression. Analyses showed that PFS was 71.6% (95% Cl 65.5–76.8%) in the daratumumab group vs 50.2% (95% CI, 43.2–65.7%) in the control group (hazard ratio of disease progression or death, 0.50; 95% Cl 0.38–0.65; p < 0.001). The ORR was 90.9% in the daratumumab group vs 73.9% in the control group (p < 0.001). CR or better was achieved in 42.6% of the patients in the daratumumab group vs 24.4% in the control group. The main adverse event observed was cytopenia and infection in the daratumumab group.

The MAIA phase 3 clinical trial[109] compared the use of daratumumab, Revlimid, and dexamethasone (DRd) to Revlimid and dexamethasone (RD) in previously untreated transplant-ineligible MM patients. DRd vs RD patients achieved better CR (47.6% vs 24.9%) and MRD (24.2% vs 7.3%) (p < 0.001). PFS at 30 months was 70.6% vs 55.6% (HR 0.56, 95% Cl 0.43–0.73, p < 0.001). The daratumumab group had a higher incidence of neutropenia (50.0% vs 35.3%) and pneumonia (13.7% vs 7.9%) than the RD group.

In the CASSIOPEIA study,[110] newly diagnosed transplant-eligible MM patients received four pre-transplant inductions and two post-transplant consolidation cycles of bortezomib, thalidomide, and dexamethasone (VTd) alone (n = 542) or in combination with daratumumab (D-VTd) (n = 543). At day 100 post-transplantation, 29% of the D-VTd group and 20% of the VTd group achieved a stringent CR (OR 1.60, 95% Cl 1.21–2.12, p = 0.001). The D-VTd group exhibited improved median PFS compared to the VTd group (hazard ratio 0.47, 95% Cl 0.33–0.67, p < 0.0001). The most observed adverse effects included neutropenia (28% in the D-VTd group vs 15% in the Vtd group), stomatitis (13% vs 16%), and lymphopenia (17% vs 10%).

Elotuzumab is a humanized monoclonal antibody against a cell surface protein called CS1 (also known as SLAMF7). This surface protein is highly expressed on MM cells, NK cells, and a subset of CD+8 T cells. The use of Elotuzumab in

combination with IMiDs and Pls has shown benefits in relapsed MM patients, however its use is limited given the availability of other active agents.[111,112]

Bispecific Antibodies

The use of novel agents and monoclonal antibody-based therapies has improved PFS of patients with MM. Bispecific antibodies include bispecific antibodies (BisAbs) and bispecific T-cell engagers (BiTEs). These molecules work by encouraging immune cells to lyse MM cells by binding antigens on MM and immune effector cells simultaneously. BisAbs are engineered antibodies, while BiTEs are recombinant proteins. Both cause T-cell activation, tumor cell lysis, and T-cell proliferation. Current bispecific antibodies target either B cell maturation antigen (BCMA), G protein-coupled receptor, class C group 5, member D (GPRC5D), or Fc Receptor-homolog 5 (FcRH5).[113–117] Table 6 summarizes various bispecific antibodies.

Bispecific Antibodies early clinical trials showed promising results with roughly 2 out of 3 heavily pre-treated patients having a response. Follow-up duration for those studies are short. Ongoing trials include products: alnuctamab[118], linvoseltamab[119], Pacanalotamab,[120] Pavurutamab,[121,122] Teclistamab,[123–125] Talquetamab,[126–128] Cevostamab[129] and Elranatamab.[130] Most of those products are being used until disease progression and this carries increased risk of infections which needs to be monitored. Phase 3 clinical trials to compare those agents to standard of care are being done and will help in comparing their promising activity with other active agents. Table 7 summarizes data of the 2 FDA-approved BCMA bispecific antibodies in MM.

Talquetamab got approved by the FDA in August 2023. MonumenTAL-1 reported data on 232 patients who received talquetamab, with 102 receiving it intravenously and 130 subcutaneously. In this phase 2 study, two recommended subcutaneous doses were tested: 405 μg per kilogram weekly (30 patients) and 800 μg per kilogram every other week (44 patients). Noteworthy side effects at these doses included cytokine release syndrome (experienced by 77% and 80% of the patients respectively), skin-related issues (reported by 67% and 70%), and dysgeusia (seen in 63% and 57%). Most cases of cytokine release syndrome were of grade 1 or 2, except for one case of grade 3 rash linked to the 800-μg dose. Response rates were evaluated at median follow-ups of 11.7 months (for the 405-μg dose) and 4.2 months (for the 800-μg dose), with response percentages of 70% (95% confidence interval [CI], 51 to 85) and 64% (95% CI, 48 to 78), respectively. Duration of response was 10.2 months and 7.8 months for the respective doses.

Chimeric Antigen Receptor T-Cell Therapy

The emergence of chimeric antigen receptor T-cell therapy (CAR T-cell therapy) has changed the landscape of treatment of patients with RRMM. The first anti-BCMA CAR T-cell therapy for MM was studied in 2013.[131] BCMA is a tumor necrosis factor receptor found on plasma cells, including MM cells. BCMA causes the proliferation and survival of MM cells through protein kinase B and nuclear factor signaling cascade.[114] Two CAR T products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), are approved by FDA for patients with RRMM, and several ongoing clinical trials are for new CAR T cell therapy as Table 8. Both are second-generation anti-BCMA therapies approved for

Table 6 Different Bispecific Antibodies Targets Used in MM

BCMA	GPRC5D	FcRH5
Teclistimab (FDA approved)	Talquetamab (FDA approved)	Cevostamab
Erranatamab (FDA approved)		
Linvoseltamab		
Alnuctamab		
ABBV-383 (TNB-383B)		
Pavurutamab		
Pacanalotamab (AMG 420)		

Table 7 Summary of the Approved BCMA Bispecific Antibodies

Variable	Teclistamab	Elranatamab
No. of patients	165	123
Dosing per study	Every week until progression	Every week initially, after six cycles (for those with at least PR for 2 mo) dosing interval changed to every other week
Inclusion criteria of study (blood markers)	Platelets ≥50 ANC>1000 Hb>8	Platelets ≥25 ANC>1000 Hb>8
Age, median (range)	64 (33–84)	68 (36–89)
Penta drug exposure	70%	71%
Penta drug refractory	30%	42%
Median prior lines (range)	5 (2–14)	5 (2–22)
EMD % (definition was different)	17% (soft tissue plasmacytomas that were not associated with bone)	32% (extramedullary and/or paramedullary with a soft-tissue component)
Prior BCMA	No	No
ORR	63%	61%
PFS	11.3 months	NR (15-mo PFS:51%)
Median follow up	14.1 months	14.7 months
DOR	18.4 months	NR (15-mo DOR: 72%)
OS	18.3 months	NR (15-mo OS: 57%)
Infections	76%	70%
G III/IV infections	45%	40%
Death (%)	68 (41%)	55 (45%)
Death due to progression	41 (25%)	37 (30%)
CRS	72%	56%
G III CRS	1%	0%
Recurrent CRS	33%	15%

Abbreviations: PR, partial response; NR, not reached; CRS, cytokine release syndrome; OS, overall survival; ORR, overall response rate; BCMA, B cell maturation antigen; PFS, progression free survival; EMD, extramedullary disease.

Table 8 Ongoing Clinical Trials for CAR-T Cell Therapy

Clinical Trials/ Study	Patients	Status	ORR (%)	Response	CRS of Any Grade (%)	Neurotoxicity (%)	Infection (%)	Reference
NCT03274219 (Bb21217)	72	Phase I	69	28% sCR+CR; 58% > VGPR	75	15%	N/A	[133]
NCT04394650 (CC-98633-MM-001)	66	Phase I	98.1	57.4% VGPR or better 29.6% CR or better	80	10.9%	N/A	[134]
NCT03070327 (MCARH17)	11	Phase I	64	N/A	40	10	N/A	[135]

(*Continued*)

Table 8 (Continued).

Clinical Trials/ Study	Patients	Status	ORR (%)	Response	CRS of Any Grade (%)	Neurotoxicity (%)	Infection (%)	Reference
NCT04309981 (ARI0002h)	35	Phase I	96.3	18.6% VGPR. 33.3 PR 44.4% sCR.	87	0	N/A	[136]
NCT04662099 (CS-1 BCMA)	16	Phase I	81	VGPR 18.75%, PR 25%, 37.5%sCR	38	0	N/A	[137]
NCT03602612 (FHVH33)	25	Phase I	92	sCR 72%	N/A	N/A	N/A	[138]
NCT 04318327 (PHE885)	31	Phase I	100	CR 17%, VGPR33%, PR 50%	93.5	3.1	N/A	[139]

patients that have previously received four or more lines of treatment, including PI, IMiD, and anti-CD38 therapy. Both are administered after lymphodepleting chemotherapy with cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2.[132]

Ide-Cel

Ide-cel showed antimyeloma activity in the phase 1 CRB-401 clinical trial.[140] In this trial, Ide-cel CAR T cells were administered to 30 patients in a dose escalation regimen—50 × 10^6, 150 × 10^6, 450 × 10^6, or 800 × 10^6 CAR T cells per kilogram. Patients administered 150 × 10^6 CAR T cells per kilogram or greater exhibited VGPR and CR, so doses of 150 × 10^6 CAR T cells per kilogram or greater were used in the subsequent phase. With the higher target dose, all patients responded, with a median PFS of 11.8 months, and CAR T cells persisted for up to 1 year after infusion.

In the phase 2 KarMMa study of ide-cel,[141] 140 patients with RRMM who had received 3 or more lines of therapy (including PI, IMiD, and anti-CD 38 directed therapy) were enrolled. Patients were 18 years or older with a median age of 61 (range 33–78), and 59% were male. Thirty-five percent of patients had high-risk cytogenetics, 94% had prior ASCT, 84% were triple refractory, and 26% were penta-refractory. Eighty-four percent of patients received bridging therapy (including dexamethasone, cyclophosphamide, daratumumab, carfilzomib, and pomalidomide) with a response in 4%. The primary endpoint was ORR, and the secondary endpoint was CR, including stringent CR. Of the 140 patients, 128 patients received ide-cel with a median follow-up of 13.3 months. ORR was 73%. Patients reaching CR were 33%, MRD negativity were 26%, and median PFS were 8.8 months. OS was 24.8 months (about 2 years). A dose–response relationship was demonstrated at the 450 × 10^6 target dose, with CR rates reaching 39%, ORRs reaching 81%, and PFS reaching 12.1 months. Depth of response and length of response were correlated in the 42 patients with a CR or stringent CR, and duration of response extended to 19, and median PFS extended to 20.2 months. The median time to first response was 1 month, ranging from 0.5 to 8.8 months, and the median time to CR or better was 2.8 months, ranging from 1.0 to 11.8 months. Data from the KarMMa trial were reanalyzed, revealing an OS of 24.8 months. Hematologic adverse events included grade 3 or 4 neutropenia in 89% of patients, anemia in 60% of patients, thrombocytopenia in 52% of patients, and leukopenia in 39% of patients. Another common adverse event, neurotoxicity, was observed in 18% of patients. Neurotoxicity reached no greater than grade 3, which only occurred in 3% of patients. CRS was observed in 84% of patients, but only 5% exhibited grade 3 or above. Within the population of treated patients (n = 128), 44 (34%) deaths were observed, 35 of which were due to progressive disease or complications resulting from progression. Treatment-related deaths were 3% and were due to gastrointestinal hemorrhage, cytomegalovirus pneumonia, pulmonary aspergillosis, and CRS.

Cilta-Cel

The CARTITUDE-2[142] phase 2 multicohort study evaluated the efficacy and safety of cilta-cel in 20 MM patients. Patients in this study had received PIs, IMiDs, anti-CD38 antibodies, and non-cellular anti-BCMA therapy. A single cilta-cel infusion was given after lymphodepletion regimen. The primary endpoint was MRD negativity, and 7 out of 20

(35%) were MRD negative at a median follow-up of 11.3 months (range 0.6–16.0) ORR was 60% (CI 95% 36.1–80.9). The median duration of response was 11.5, and PFS was 9.1 months. Twelve patients (60%) had CRS (grade 1–2); four patients had immune effector cell-associated neurotoxicity (two had grades 3–4). Seven (35%) patients died, three due to progressive disease and four due to adverse events, one of which was treatment-related. Overall, patients with RRMM showed a favorable response to cilta-cel. Process of collection of CAR T cells, manufacturing and infusion are summarized in Figure 2.

Recently, both Idel-cel and Cilta-cel were studied in separate phase III clinical trials in KarMMa-3 and CARTITUDE-4 studies summarized in Table 9.

New Developments

OS and PFS of MM have improved with new drugs, but 20–25% of newly diagnosed MM patients and 50% of patients with RRMM do not respond to PI.[144] Thus, new drugs or combinations are needed.

Bcl-2 and Mcl-1 are therapeutic targets in the treatment of MM. Venetoclax is effective in patients with t(11; 14) and high Bcl-2 expression.[145] Mcl-1 is reported in MM associated with 1q21 amplification. The overexpression of Mcl-1 is associated with poor prognosis.[146] Several clinical trials of Mcl-1 inhibitors like MIK 665, PRT1419, and AMG 176 are currently in phase 1, as shown in Table 10. Maritoclax is a selective Mcl-1 antagonist that causes caspase-3 activation by direct binding to Mcl-1 and causes proteasomal degradation.

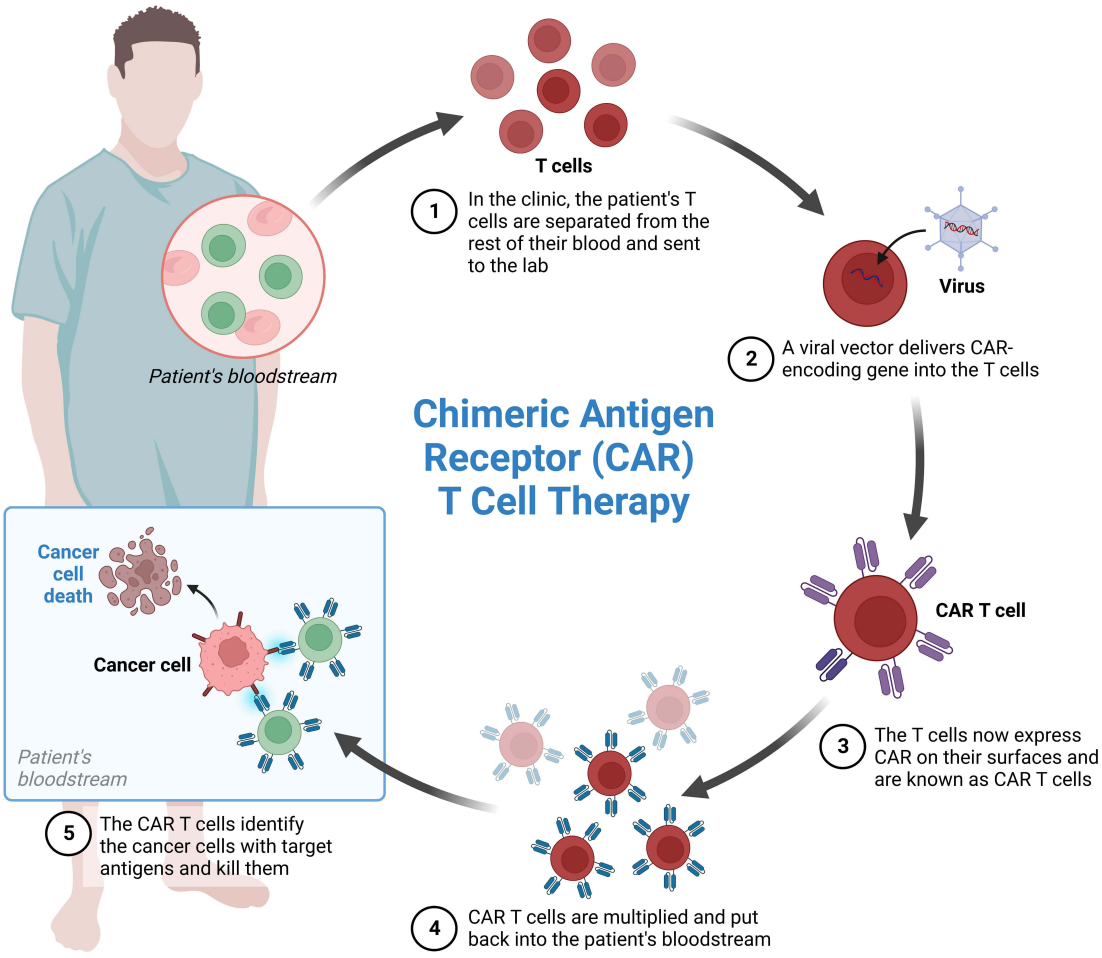

Figure 2 Mechanism of CAR T cell therapy in MM. It includes collection of T cells, multiplication and infusion to patient.
Notes: Adapted from Parikh RH, Lonial S. Chimeric antigen receptor T-cell therapy in multiple myeloma: A comprehensive review of current data and implications for clinical practice. *CA*. 2023;73(3):275–85. © 2023 The Authors. CA: A Cancer Journal for Clinicians published by Wiley Periodicals LLC on behalf of American Cancer Society.[143]

Table 9 Summary of Phase III Trials of CAR-T Cell Therapy in Multiple Myeloma

Variable	KarMMa-3	CARTITUDE-4
Number of patients	386	419
Median age (years)	63	61.5
Prior lines of therapy (median)	3	2
Triple class refractory	65%	14%
Refractory to anti-CD38	95%	24%
Median follow up (months)	18.6	15.9
ORR	71%	84.6%
PFS (median)	13.3 months	NR
12-months PFS	55%	75.9%

Table 10 Ongoing Trials of New Therapies for Multiple Myeloma

Drug	Target	Phase	Clinical Trial	Reference
MIK 665	BCL-2-Mcl-1 inhibitors	Phase 1	NCT04702425	[147]
PRT1419	Mcl-1 inhibitors	Phase 1	NCT04543305	[148]
AMG 176	Mcl-1 inhibitors	Phase 1	NCT02675452	[149]
Ibrutinib	BTK inhibitors	Phase 1	NCT03702725	[150]
Acalabrutinib	BTK inhibitors	Phase 1	NCT02211014	[151]
Anti-BCMA CAR-NK	NK cells	Phase 1	NCT03940833	[152]
Anti-BCMA CAR-NK	NK cells	Phase 1	NCT05008536	[153]

Bruton's tyrosine kinase (BTK) is overexpressed in MM cells and stem cells.[154] Ibrutinib and acalabrutinib are two FDA-approved BTK inhibitors for the treatment of B-cell malignancies that are being investigated in clinical trials for MM, as shown in Table 10.[155]

Anti-BCMA CAR-T has promising results in MM, but there are concerns about toxicity, including CRS, neurologic toxicity, and bone marrow suppression.[156] Therefore, NK cells can be an option.[157] Trials of NK CAR T cells and several other clinical trials are currently ongoing, as shown in Table 8

Modakafusp is an immunocytokine that is aimed at delivering interferon alpha-2b to CD38+ cells. In a phase 1 clinical trial, 83 patients with RRMM (at least 3 previous lines of treatment) received 1- to 4-hour madakafusp infusions of 11 doses from 0.001 to 6 mg/kg following a 3+3 dose-escalation design. ORR was 42%. The median PFS was 5.7 months. Modakafusp showed promising antimyeloma activity in extensively pretreated MM patients, including those that were anti-CD38 refractory.[158]

Conclusions

It is important to differentiate between different forms of plasma cell dyscrasias and related disorders as delaying treatment or missing diagnosis has dire outcome. With wide availability and use of new imaging techniques including PET-CT and MRI, patients benefit from early treatment.

With the emergence of many new treatments, the future of MM therapy is bright. The introduction of immunological agents has revolutionized MM treatment with good efficacy and tolerable toxicity profile. Anti-CD38 drugs, like daratumumab, can be the backbone of MM treatment in both upfront newly diagnosed MM and relapsed refractory settings. Isatuximab is a new-generation anti-CD38 and an addition to this group.

New immunotherapeutics (CAR-T and bispecific antibodies) are promising treatment options in heavily treated RRMM settings. It is possible that armed immunotherapy can challenge the current standard of care and is a great option for high-risk MM. Other immunomodulators, such as antibody-drug conjugates and cereblon E3 ligase modulators, will continue to strengthen the field of various immune-based treatments. Non-immune-based treatment regimens must continue as patients on immunotherapy will relapse.

Despite significant development in the therapeutic modalities of MM, many patients relapse and develop drug resistance. Novel targeted therapies with great safety and efficacy are needed to combat MM, and a better understanding of the genetic and epigenetic basis of MM is the key. Next-generation sequencing coupled with genome editing will improve prognostication, risk stratification, and therapy response prediction. These methods will also help in the discovery of new strategies to prevent drug resistance as well as to improve the outcomes of MM.

Disclosure

The authors report no conflicts of interest in this work.

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