[Short title + Author Name - P&H title] 31 (2024) 103920

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Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

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Review

An overview of multiple myeloma: A monoclonal plasma cell malignancy's diagnosis, management, and treatment modalities

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ARTICLE INFO

Keywords:
Myeloma
Diagnosis
Immunomodulatory drug
Proteasome inhibitors

ABSTRACT

Multiple Myeloma (MM) is a plasma cell cancer with high mortality and morbidity rates. Its incidence rate has increased by 143% since 1975. Adipokines, cytokines, chemokines, and genetic variations influence the development and progression of MM. Chromosomal translocations cause mutations associated with MM. The pathogenesis of MM is complicated by novel issues like miRNAs, RANKL, Wnt/DKK1, Wnt, and OPG. Conventional diagnosis methods include bone marrow biopsy, sPEP or uPEP, sIFE and uIFE, and sFLC assay, along with advanced techniques such as FISH, SNPA, and gene expression technologies. A novel therapeutic strategy has been developed recently. Chemotherapy, hematopoietic stem cell transplantation, and a variety of drug classes in combination are used to treat patients with high-risk diseases. Alkylating agents, PIs, and IMiDs have all been developed as effective treatment options for MM in recent years. This review overviews the current recommendations for managing MGUS, SMM, MM, SP and NSMM and discusses practices in diagnosing and treating MM.

1. Introduction

Multiple myeloma is a hematologic malignancy characterized by abnormal plasma cells in bone marrow inducing destructive bone lesions. This disease causes overpopulation of abnormal clonal plasma B cells in bone marrow, bringing downregulation of osteoblasts and activation of osteoclasts, which induce malignant bone lesions, kidney injury, anemia, hypercalcemia, and painful fractures (Antoine-Pepeljugoski & Braunstein, 2019). Bone deterioration, hematopoietic dysfunction, and end-organ failure are the most prevalent signs of excessive monoclonal protein synthesis (Eslick & Talaulikar, 2013; Gau et al., 2022; Walker et al., 2014). Multiple Myeloma (MM) is the second most common hematologic cancer. It involves abnormal proteins and increased plasma B cells in the bone marrow. MM is influenced by demographics, physiology, clinical risk factors, and various treatment approaches(Kundu et al., 2022); MM contributes to up to 10 % of hematologic neoplasms. Less than two-thirds of people under 40 seem to experience it more regularly than people over 40, and the median age of diagnosis is 65 years (Agarwal & Ghobrial, 2013). In 1848, Solly made the first identification and description of MM; it was discovered that MM belongs to a spectrum of illnesses, including plasma cell leukemia and abnormal production of M−protein of unidentified consequence called MGUS(Ribourtout & Zandecki, 2015). MGUS, clinical MM, smouldering multiple myeloma (SMM), and, infrequently, plasma cell leukaemia are just a few of the illnesses that fall under the umbrella term "plasma cell neoplasia"(Hoffman et al., 2013). A significant fraction of abnormal antibodies areare produced. These are also called monoclonal arterial antibodies, classified as light chains or Bence-Jones proteins (Cook & Macdonald, 2007). An elevated paraprotein level of up to 30 g/L on serum electrophoresis confirmed the diagnosis of MM, which was approved by an increased plasmacytosis of hematopoietic stem cell biopsy, it's approximately above 10 % (Cook & Macdonald, 2007; Eslick & Talaulikar, 2013).

Cancerous cell proliferation in bone marrow disrupts blood cell and antibody production, leading to osteolytic lesions, soft bone patches, and increased risk of osteopenia, osteoporosis, and fractures (Sandal et al., 2018). Although they exist, these osteolytic abrasions and other diagnostic symbols of bone damage are not always present in MM patients (Kundu et al., 2022). Numerous possible risk factors, including radiotherapy, environmental pollutants, chronic antigen activation, and genetics, contribute to the multistep process by which this progressive plasma cell tumor with a stable clone can develop malignancy(Bird

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https://doi.org/10.1016/j.sjbs.2023.103920
Received 25 July 2023; Received in revised form 20 December 2023; Accepted 29 December 2023
Available online 30 December 2023

et al., 2011). Recent advancements in understanding the cellular and molecular causes of MM have led to the development of effective treatments, including chemotherapy, stem cell transplantation, and various drug classes such as corticosteroids, anti-cancer drugs, proteasome inhibitors, and immunomodulatory drugs (Bird et al., 2011; Eslick & Talaulikar, 2013; Poczta et al., 2021; Walker et al., 2014). The current information on MM is alarming; patients in stage III of the disease have an average life expectancy of 29 months, as opposed to those in stages I and II, who have average survival periods of 5 and 4 years, respectively (Leong et al., 2023). The progression of MM without treatment could eventually end with organ damage(Bianchi & Anderson, 2014). Since the emergence of cutting-edge medicines, survival rates for MM have significantly increased. As MM is a curable cancer, several novel treatments that have the potential to be developed are accomplished for the medication(Firth, 2019). Targeted drugs like PIs and IMiDs, combined with autologous stem cell transplantation and high-dose Melphalan, have significantly improved outcomes for MM patients in the past two decades (Holstein et al., 2018; Poczta et al., 2021).

The tremendous response rate to these breakthroughs has increased the overall probability of survival (Agarwal & Ghobrial, 2013). Two monoclonal antibody-based anti-myeloid medications, daratumumab and elotuzumab, were approved by the Food and Drug Administration (FDA) in 2015. These medications profoundly changed the paradigm of MM therapy options (Braunstein et al., 2021; Zhang et al., 2017). Rituximab, antibody-drug conjugates like belantamab mandolin, and idecabtagene vicleucel are just a few of them that have gained approval over time (Braunstein et al., 2021; Jiao et al., 2020). More immunotherapeutic drugs, such as CART-cells, are being evaluated in phase 2 for use in patients with relapsed or resistant MM; participants exhibited profound and protracted reactions during treatment (Berdeja et al., 2021; Usmani et al., 2021). Thalidomide and its analogues, lenalidomide and pomalidomide, are IMiDs used in MM treatment, known for their antiangiogenic activity. IMiDs are commonly combined with PIs, steroids, and monoclonal antibodies (Gao et al., 2020). Thus, a comprehensive understanding of MM's epidemiology, etiology, pathophysiology, diagnostics, and treatment approaches is crucial. Recent breakthroughs in MM diagnosis and therapy promise to improve the current situation.

2. Incidence and mortality rate

According to the most recent data from the Global Cancer Observatory (GLOBOCAN), 0.9 % of all cancer diagnoses and an estimated 588,161 cases of MM worldwide are reported each year (Bray et al., 2018; Cowan et al., 2018, 2022). About 90,000 male and 70,000 female patients had an age-standardized incidence of 2.1/100,000 and 1.4/100,000, respectively, of those instances (Bergsagel & Anderson, 2004; Cowan et al., 2018). From birth to age 74, men have a cumulative risk of 0.24 %, and women have a cumulative chance of 0.17 %, making men around 1.5 times more likely than women to be diagnosed with the illness (Rosko et al., 2017). Between 1990 and 2016, the prevalence of MM increased by 126 % worldwide. In 2016, 2.3 million dollars were incurred in MM-adjusted lifetime years with a disability (Bergsagel & Anderson, 2004; Zhou et al., 2021). In civilized countries, the most significant, most incredible incidence rate such as Western Europe, Australia, and the United States most effective, such as Western Europe, Australia, and the United States (US) was observed. In 2020, it was projected to see 32,000 cases, or 1.8 % of all diagnosed cancer in the US, as mentioned in Fig. 1 (Cowan et al., 2018; Hemminki et al., 2021). As a result, MM is currently described as the 14th most frequent neoplasm. Today's expected incidence rate is 7.0/100,000, a 143 % increase from 1975's predicted incidence rate of 4.9/100,000 (Cowan et al., 2018). According to age-standardized mortality, there were 59,000 male and 47,000 female deaths, totalling 1.3/100,000 male deaths and 0.9/100,000 female deaths yearly. The likelihood of dying from MM was 0.15 % for men and 0.10 % for women, suggesting a comparable global survival rate. Between 1990 and 2016, neoplasm-related deaths increased globally by 94 % (Padala et al., 2021). Higher survival rates have decreased overall mortality rates for multiple myeloma over the past few decades. From 2013 to 2017, the mortality rate fell from 3.3/100,000 to 3.2/100,000 for all age groups and from 21.7/100,000 to 20.5/100,000 for age groups over 65, as reported by the SEER project (Padala et al., 2021; Turesson et al., 2018). Approximately 5 % of diagnoses are localized illnesses with a 5-year survival rate of 74.8 %. The remaining 95 % are systemic MM, with a 5-year survival rate of 52.9 %. The stage of diagnosis can impact survival rates (Tang et al., 2020). Patients with this condition had greater rates of illness, such as heart failure, anemia, and leukocytosis (Padala et al., 2021; Turesson et al., 2018).

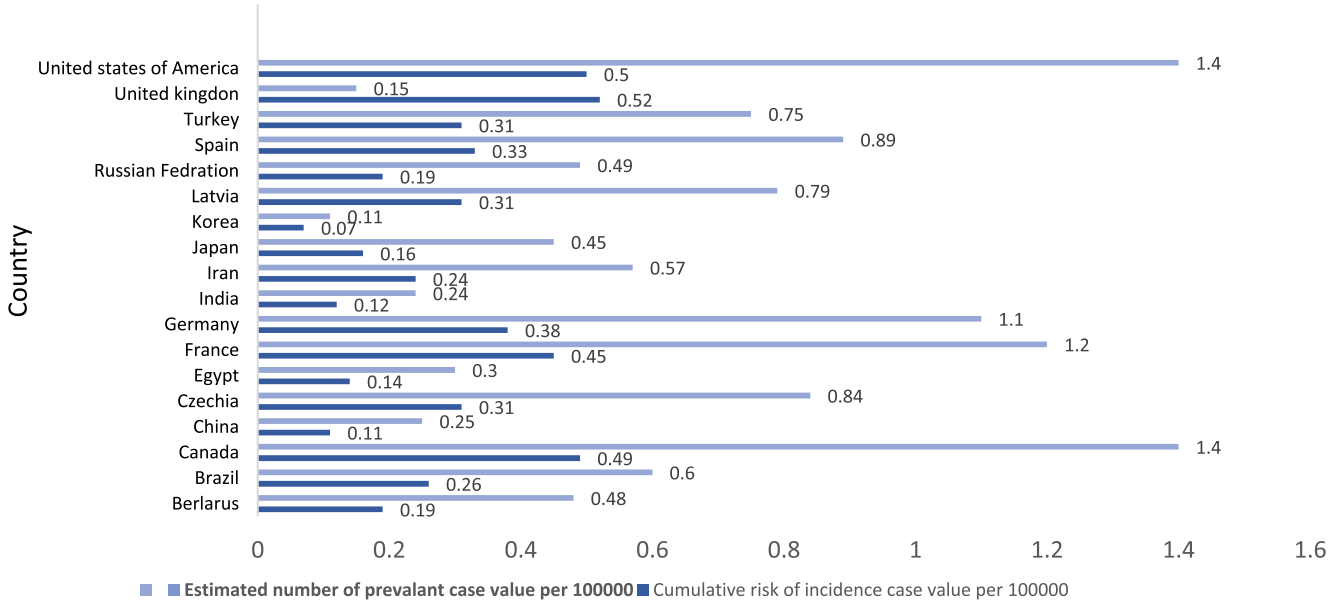

Fig. 1. Graph illustrating the predicted cumulative risk of incidence and prevalence of multiple myeloma for both sexes. The presented data were retrieved from the GLOBOCAN report published in 2018 (Siegel et al., 2023).

Novel therapeutic drugs have considerably increased patient survivability in the past 20 years, but the disease is still incurable, and the average overall life probability of patients with a new diagnosis is only about 6 years (Gau et al., 2022). The median overall survival for MM patients over 70 is around 5 years. On average, MM patients have a duration of persistence of nearly 6 years with current therapy (Rajkumar, 2022). The average life expectancy is more than 8 years, even though patients who qualify for autologous stem cell transplantation (ASCT) have 4-years survivorship of more than 80 % (Durie et al., 2020; Terpos et al., 2013).

3. Pathophysiology and molecular biomarkers

MM's origin remains unknown; however, analysis shows frequent translocation and alteration in gene promoters in chromosome 14which play an essential role in MM development (Thorsteinsdóttir et al., 2023). MM can occur in individuals without known risk factors and is influenced by multiple factors. Pathophysiology refers to changes in body functions caused by MM. The pathogenic process starts with forming clonal plasma cells, or MGUS, which precede MM. Light-chain MGUS is a precursor to Light-chain MM and is characterized by abnormal κ/λ FLC ratio, increased Light-chain concentration, and absence of monoclonal heavy-chain expression in screening tests (Dispenzieri et al., 2010; Kyle et al., 2018). It was observed that patients with MGUS IgG or IgA progress to MM (Dispenzieri et al., 2010; Kyle, 1978; Weiss et al., 2009). Patients with MGUS don't exhibit any symptoms or end-organ damage but risk about 1 % of getting MM or an associated cancer yearly (Kazandjian, 2016). Compared to normal bone remodelling, MM's connecting mechanism between osteoclasts and osteoblasts is not entirely known (Kristinsson et al., 2011; Terpos et al., 2018). MM research focuses on how the bone marrow microenvironment contributes to the progression of the disease. The bone marrow niche's microenvironment can have the ability to repair damage and react to external stimuli by producing inflammatory mediators and endocrine signals (Reagan & Rosen, 2016). The bone marrow microhabitat plays a substantial part in malignant transformation and the onset of MM illness by facilitating drug resistance infiltration and growth, proliferation, adhesion, migration of malignant cells, and cytotoxicity of healthy cells (Reagan & Rosen, 2016). Additionally, it was discovered that the bone marrow microenvironment activates the provocative arbitrators' reactive oxygen and nitrogen species, which promotes MM's growth and progression. The development of MM is significantly influenced by adipokines, cytokines (IL-6), chemokines, and vascular endothelial growth factors (VEGF) (Al-Mansoori et al., 2022). The heavy chains of immunoglobins switch their regions on the long arm of chromosomes 14, causing genetic variations and mutations such as translocation t (4;14), t(14;16), t(14;20), deletion in 17p, gain in 1q, or p53 strongly associated with the incidence of MM (Rajkumar et al., 2014; Terpos et al., 2018). regular Furthermore, the bone marrow microenvironment affects the transition from the asymptomatic stage of MGUS to triggering MM incidence. Extracellular vesicles containing RNA, metabolites, proteins, DNA, and phospholipids are released by bone marrow cells, which modify the cell by removing them into the surrounding environment, as Van Niel et al. recently found in 2018 (Van Niel et al., 2018). Numerous research studies have focused on the biological effects of MM exosomes and extracellular vesicles on cells in the bone marrow microenvironment (Harshman et al., 2016). It was discovered that IL-6, which inhibits osteoblastic growth and contributes to the disease, is secreted by bone marrow stromal cells, which are the MM cell-derived exosomes (Liu et al., 2020). As a result, MGUS was brought on by a dysregulation of the normal plasma cells (Gao et al., 2020). A mutational burden also produces an intermediate known as smouldering multiple myeloma (SMM) (Walker et al., 2014). In literature, disease evolution from MGUS to SMM to MM depends on plasma cells' complex genomic alterations associated with reprogramming the bone marrow microenvironment. It has been demonstrated that the cause of MM is a molecular change disturbing plasma cells (García-Ortiz, 2021; Jagannath et al., 2018).

Another imbalance of malignant plasma cells in the bone marrow is the cause of non-secretory multiple myeloma (NSMM) (Corso & Mangiacavalli, 2017). Furthermore, recent research has linked the progression of NSMM to MM to epigenetic changes such as aneuploidy, single nucleotide variants, chromosomal translocations, small deletions and insertions, and the copy number of variants inducing mutations on genes (Dutta et al., 2019). Few other studies have discovered that several gene mutations related to the induction of MM are MMKRAS, BRAF, FAM46C, NRAS, TP53, and DIS3 (Dutta et al., 2019; Schürch et al., 2020). However, the clonal progression associated with MGUS, SMM, or NSMM into MM remains poorly understood, and it is highlighted that the bone marrow microenvironment plays an essential role in regulating and induction these pathologies (Schürch et al., 2020). The mechanistic beginning and development of MGUS, SMM, and MM are summarized in Fig. 2.

Even though MM is a hereditary disease, some studies have revealed that in the early stages of the disease, the bone marrow microenvironment is altered by developing a permissive environment, resulting in phenotypic instability and genetic changes as a result of the disruption of niche in the bone marrow microenvironment (Capp & Bataille, 2022). The niche is critical in instigating cancer development through its effects on genetic and epigenetic instability. In the past few decades, research on MM and MGUS has been classified as a stochastic process involving random genetic and epigenetic instability in the bone marrow microenvironment, equivalent to tissue disruption-induced cellular stochasticity in cancer development (Capp & Bataille, 2018, 2020). In the early stages of MM, the inflammation response induced is IL-6 dependent (Capp & Bataille, 2022). Kyle et al. discovered in 1978 that the disorder allowed the discovery of monoclonal proteins in the blood, patients without any symptoms, and end-organ damage was described as a benign monoclonal gammopathy (Oben et al., 2021). Diagnosing this pathology was possible with blood serum protein electrophoresis to regulate the concentration of M−proteins immunoglobulins (Ig) and with microscopy to set up the plasma cell percentage in bone marrow aspirates to allow for MM progression. Meanwhile, low-input whole-genome sequencing (WGS) technology avoids contamination by normal plasma cells and allows a better definition of MGUS, SMM, and NSMM (Oben et al., 2021).

3.1. Pathogenesis of targeted tissue markers of MM

Numerous tissues, including bones, blood, kidneys, and even the nervous system, can be targeted by MM, leading to very severe complications that may finally result in organ damage (Terpos et al., 2018). According to various research on skeletal development, more than 80 % of MM patients have debilitating bone abrasions and neurological abnormalities that cause fractures, pain, and mobility problems (Hameed et al., 2014). Osteoclast and osteoblast activity should typically be balanced to achieve bone remodelling. Osteocytes cause this pattern, but individuals with MM have less of them, disrupting bone remodelling and leading to fractures and discomfort in their bones (Reagan & Rosen, 2016). Numerous studies using MM cell lines and from a molecular perspective demonstrate that the pathogenesis of MM is complicated by several novel issues, along with the NF-kB ligand (RANKL) pathway, the dickkopf-1 (Wnt/DKK1), the wingless (Wnt), and the osteo-protegrin (OPG) route (Fig. 3). The development of MM in the skeletal system is also characterized by enhanced osteoclastic activity after bone resorption and decreased osteoblastic capability, which results in diminished or nonexistent bone production (Rasch et al., 2020). Increased osteoclastic activity in MM patients causes a rise in bone adhesion markers (Capp & Bataille, 2020). Numerous chemokines are involved in MM, including SDF-1, MIP-1, IL-3, IL-6, IL-7, and VEGF (Fan & Podar, 2021; Papy-Garcia & Albanese, 2017).

The average endurance rate of patients with MM is decreased by

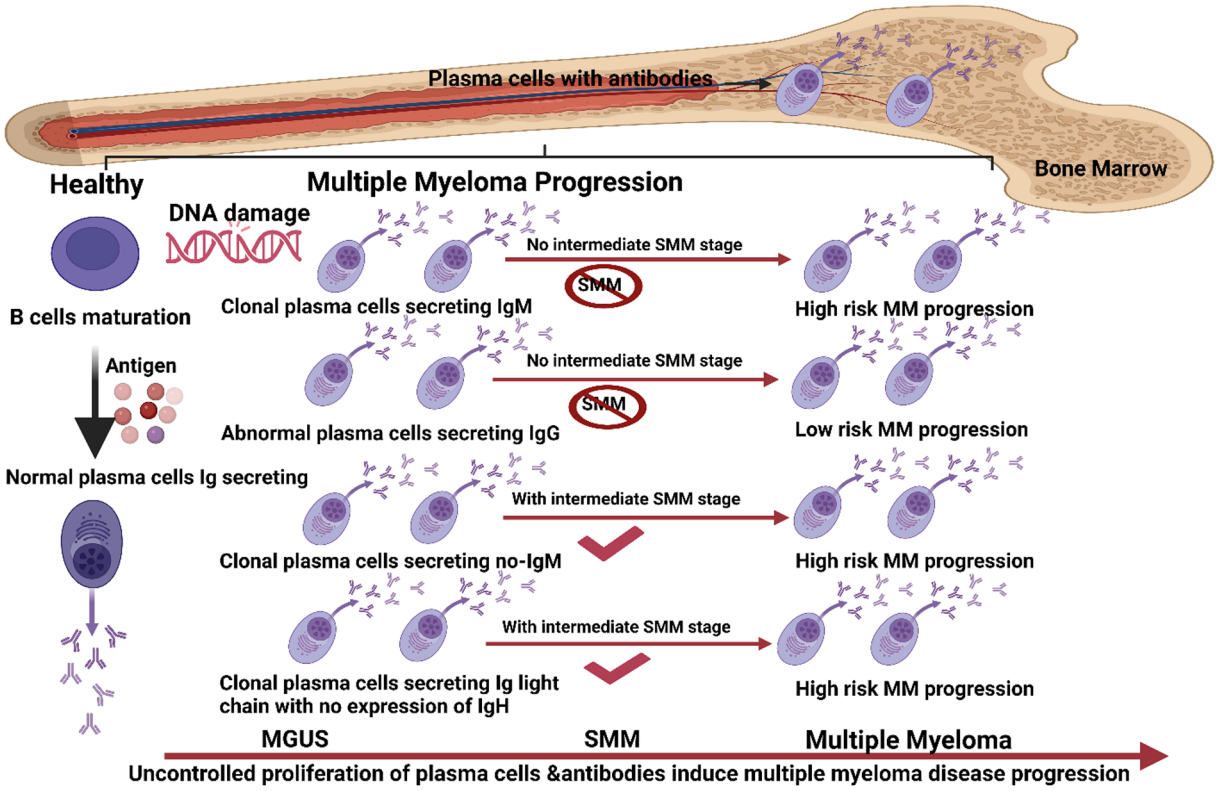

Fig. 2. The mechanism of development and progression of multiple myeloma: All kind of MM originates as MGUS due to multiple primary genetic mutations such as chromosomal abnormalities or IgH translocation that affect the targeted genes (e.g., MMKRAS, BRAF, FAM46C, NRAS, TP53, and DIS3) give rise to SMM (an intermediate stage). If abnormal clonal plasma cells produce IgM, IgL (Ig light-chain) with no expression of IgH have a higher risk of MM.

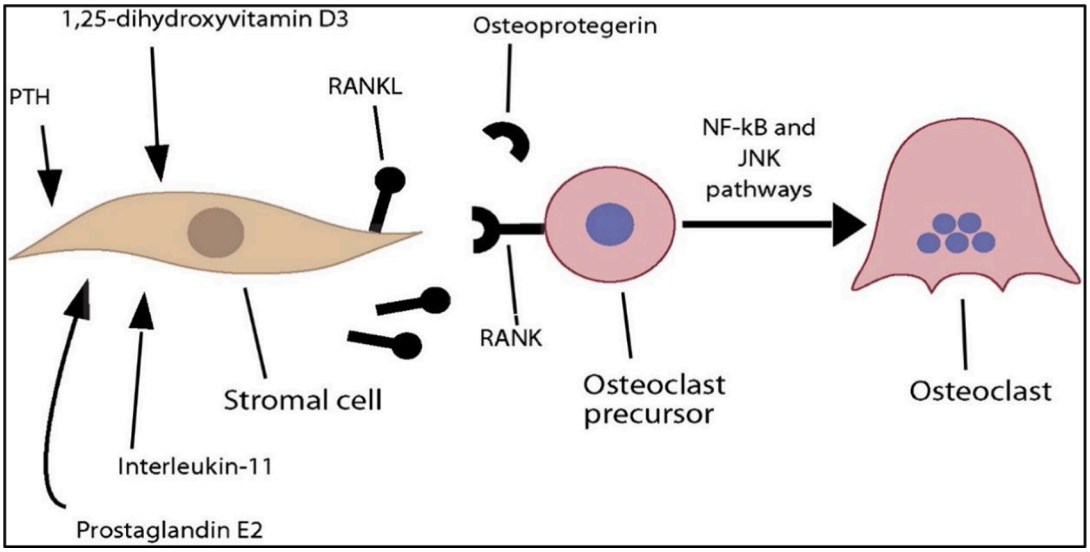

Fig. 3. Osteoclasts are produced by bone marrow stromal cells that express nuclear factor-kB ligand-receptor activators (RANKL). These activators are triggered by osteotrophic substances involved in osteoclasts' maturation and differentiation (Lentzsch et al., 2007).

renal involvement, the most frequent malignancy associated with end-stage renal failure (Corradetti et al., 2021). Specific antibody light chains have toxic effects on renal structures, primarily renal tubules and less frequent glomeruli, causing renal failure in MM patients (Mussap & Merlini, 2014). Renal insufficiency can occasionally be caused by hypercalcemia. Monoclonal light chains, a type of immunoglobulin, have toxic effects on the renal tubules and glomeruli, the primary factor of kidney dysfunction in myeloma patients. Other variables that may accelerate the disease's progression include dehydration, the application of contrast mediators, and the use ofnephrotoxic drugs (such as antibiotics and nonsteroidal anti-inflammatory drugs) (Mussap & Merlini, 2014). They are rarely the main factor causing renal failure, but they frequently contribute to making the harmful consequences of light chains worse. Numerous nephrons, glomeruli, tubule, interstitium, and blood artery structures are damaged by monoclonal light chains, resulting in various pathologic and clinical symptoms (Madan et al., 2010; Mussap & Merlini, 2014). The most frequent kind of renal injury is myeloma-induced nephropathy, sometimes called the "myeloma

kidney." Other clinicopathological disorders include acquired adult Fanconi syndrome, amyloidosis, and light chain deposition disease (LCDD). Renal dysfunction is linked to monoclonal gammopathy. The most frequent histological pattern is nephropathy, which accounts for around 40 % of the characteristics after a kidney biopsy (Zhang et al., 2023).

Plasma cells have been discovered in the urine of MM patients, which indicates that the condition significantly affects the production of blood cells (Mussap & Merlini, 2014). Hematologically, individuals with MM have uncontrollably expanded cells, notably plasma cells, resulting in many abnormal cells. Blood pathology signs, such as anemia, and thrombocytopenia, are connected to MM disorders (Fan & Podar, 2021). Neurological conditions, such as nerve system impairment, affected about 1 % of MM patients. It may be related to white blood cells entering the cerebrospinal fluid, the CNS, or the meninges, which are sheaths covering the brain and vertebral column, after overcoming neuronal barriers.

3.2. *miRNA-based biomarkers in MM pathogenesis*

In the post-genomic era, a variety of miRNAs have been identified as potential biomarkers of MM pathogenesis; miR-1, miR-15, miR-16, miR-124a, miR-125b, and miR-133a activity were shown to be reduced in bone marrow cell lines and patient samples than in healthy samples, according to earlier research (Qu et al., 2013). Furthermore, chronic lymphocytic leukemia (CLL) and MM are anticipated to indicate a substantial probability of deletion of the 13q14 region of the chromosome. On chromosome 13q, miR-15a and miR-16 are both found. Their expression in MM plasma cells is noticeably decreased than in normal bone marrow tissues (Lerner et al., 2009). By reducing the expression of cyclin D1 and D2 CDC25A, key producers for MM multiplication,iR-15a and miR16 have been discovered to limit cell growth in vitro (Roccaro et al., 2009). This is achieved by blocking the NF-kB/AKT3 and BCL-2 pathways to target apoptotic processes. Furthermore, miR-21 expression in MM plasma cells is higher than in other normal cell types, and miR-21 has an oncogenic potential and can be a target for MM patients (Leone et al., 2013).

Numerous arguments have been made to support the idea that this miRNA is oncogenic, including the claims that IL-6 precisely STAT3-dependently induces miR-21 expression. In the absence of IL-6, ectopic miR-21 expression in MM cells lowers apoptosis, and miR-21 inhibition inhibits the growth of MM cells (Handa et al., 2019; Pichiorri et al., 2008). Another study found a negative correlation between MCL-1 mRNA transcript levels and miR-29a/b expression levels in patient samples and other MM cell lines (Qu et al., 2013). Given that treatment-resistant MM cells overexpress MCL-1, which shows that it may be a significant factor in anticancer drug resistance, MCL-1 has the potential to be a therapeutic target. While miR-221 and miR-222 target the drug sensitivity-related pro-apoptotic PUMA and the tumor suppressor PTEN to demonstrate their oncogenic function, miR-92a has been proposed to have a potential association with the emergence of MM via stimulation of the c-Jun pathway (Bird et al., 2011; Leone et al., 2013; Papanota et al., 2021; Zhao et al., 2015). The development of MM therapeutic options is appealing due to the regulatory roles that miRNAs can play in modulating post-transcriptional genes. Additional research is necessary to fully comprehend these pathways and facilitate the reliable application of miRNAs in the clinic. Different microRNA types are depicted in Fig. 4 and how they relate to the pathogenic characteristics of MM.

4. Signs and symptoms

MM is an insidious pathology that can present severe symptoms and is often observed in older adults with a variety of symptoms CRAB (hypercalcemia, renal dysfunction, anemia, bone pain with lytic lesions). In newly MM patients diagnosed, the most common symptoms observed were weight loss (24 %), hypercalcemia (28 %), fatigue (32 %), elevated creatinine (48 %), bone pain (58 %) and anemia (73 %); they could be vague and vaguely recognizable as those from other disorders (Cowan et al., 2023). Lethargy, exhaustion, infection, weight loss (cachexia), and loss of appetite (anorexia) are the more common signs and symptoms, as are bone pain, weariness, and infection (Bird et al., 2011). When diagnosing MM in asymptomatic people, laboratory findings, including metabolic alkalosis, anemia, or proteinuria, are more likely to be employed. Osteoporosis, osteolytic lesions, pathological fractures, hypercalcemia, and the growth of plasma cell tumors

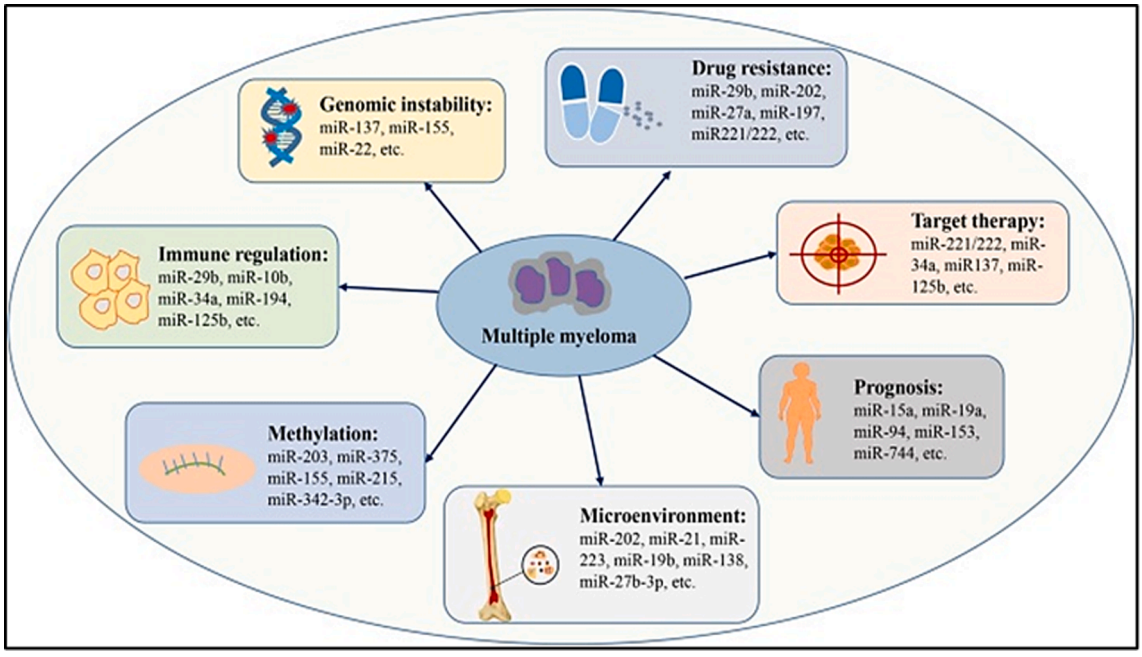

Fig. 4. A key role in regulating the pathological processes nd potential prognostic biomarkers and therapeutic targets asdiscovered by examining the correlations between various microRNA types and the hallmarks of multiple myeloma pathogenesis (Handa et al., 2019).

(plasmacytoma) are examples of clinical signs affecting the muscular system (Kristinsson et al., 2011). Most MM patients experience bone pain, affecting the spine, ribs, and lower limbs (Grønningsæter et al., 2018). These issues are the key contributors to reduced cognition and a lower quality of life (Monge et al., 2020). Cryoglobulinemia, thrombocytopenia, prolonged bleeding time, coagulopathy, and anemia are pathological indicators of the blood system. Anemia is a typical symptom brought on by bleeding; the process creates suppression, high amounts of paraprotein in the body, and impaired renal function. These consequences or manifestations while writing a complete description emphasising the signs (Monge et al., 2020). The renal system is characterized by urinary tract infections (UTI), acute gouty arthritis, electrolyte imbalance, glomerulonephritis, and nephrotic diseases linked to amyloidosis. Bence-Jones protein found in urine, hypercalcemia, hyperuricemia, and amyloidosis, additional variables affecting renal function in MM patients.; common variable immunodeficiency (CVID) and recurrent illnesses are symptoms of the immune system (Scarpa et al., 2020; Yavorkovsky & Hope, 2020). Contraction of the spinal column and peripheral nerves, neuropathic pain brought on by tumor infiltration and associated with adverse health effects disorder, epicondylitis brought on by amyloidosis, and poor cognitive function brought on by hyper-viscosity and hypercalcemia are just a few examples of neurological comorbidities (Nau & Lewis, 2008). The most effective way to identify other symptoms is through a physical examination. Most MM patients experience normal physical signs of the illness (Nau & Lewis, 2008). According to data shown in Fig. 5, people who undergo clinical tests for possible MM exhibited the highest provocative result.

5. Clinical manifestations

Bone involvement is a necessary part of the diagnosis. The following tests could diagnose MM straightforwardly (Table 1).

5.1. Unspecified consequence of monoclonal gammopathy of undetermined significance (MGUS)

According to the M−protein isotype, MGUS disease can be recognized by the occurrence of M−proteins or by an abnormal free-light chain (FLC) proportion in peripheral blood (Kyle, 1978). The monoclonal spike concentration (M−spike) must exceed 3 g/dl. The ratio must be more than 100, employing a combination of serum-based protein assays by electrophoresis (SPEP), immunofixation, and serum FLC assays to determine M−protein concentration(Terpos et al., 2013). The bone marrow contains 10 % and 60 % of plasma cells, and the M−spike protein is 3 g/dl or higher, as mentioned in Table 2. A bone marrow biopsy and a clinical interpretation of the findings by microscopy to establish the extent of malignant plasma cells in the bone marrow can both be used to demonstrate a plasma cell abnormality. This percentage needs to be greater than 10 % to indicate MGUS disease. Recent research has shown that patients diagnosed with MGUS before being given the MM diagnosis had a 15 % higher chance of surviving the disease (Goyal et al., 2019).

Table 1
Conventional and advanced methods for the diagnosis of multiple myeloma.

Conventional method	Plasma cell count is done together with a complete blood count (CBC) Level of calcium in serum Electrophoresis of proteins in serum and urine (Cowan et al., 2022; Fleming et al., 2017)
Advanced methods	Free heavy chains in a serum-free light-chain assay (a relatively large proportion of FLC, with few or no Ig molecules, absence of free or connected light chains) CT- Scan and MRI scans FISH Cytogenetics and fluorodeoxyglucose-positron emission tomography (FDG-PET) (Tagliafico, 2021; Tan et al., 2013)

The three subtypes of MGUS are non-IgM MGUS, IgM MGUS, and light chain MGUS (LC-MGUS) (Table 2) (Wadhera et al., 2011; Wadhera & Rajkumar, 2010). Researchers have discovered that patients with non-IgM MGUS (IgG, IgA, and IgD) account for most MGUS cases and are more likely to acquire MM. The literature described that the second subtype of MGUS, IgM MGUS, can develop into immunoglobulin light chain amyloidosis (AL), lymphoma, or Waldenstrom macroglobulinemia (Dispenzieri et al., 2010). IgM MGUS hardly ever progresses to MM. Patients with LC-MGUS are characterized by a monoclonal protein with an Ig heavy chain deficiency and observed a progression to light chain deposition disease, light chain PCM AL amyloidosis and idiopathic Bence Jones proteinuria. In several studies, the advancement of LC-MGUS patients into MM is around 0.3 % (Dispenzieri et al., 2010; Nau & Lewis, 2008).

5.2. Smoldering multiple myeloma (SMM)

Premalignant SMM lacks the symptoms of the actual disease but changes several blood proteins and increases blood plasma cells in the bone marrow. However approximately 50 % of people with multiple myeloma will develop the disease again within 5 years (Mateos & San-Miguel, 2018). When the concentration of M protein is greater than 3 g/dL, or the malignant plasma cells in bone marrow ratio is 10 %, and there are no signs of organ damage, SMM is determined by IgG or IgA (Romano et al., 2020). SMM patients are categorized as being in an intermediate phase between MGUS and MM based on higher bone marrow plasma cells (10 %) in patients who stayed stable for 5 years without

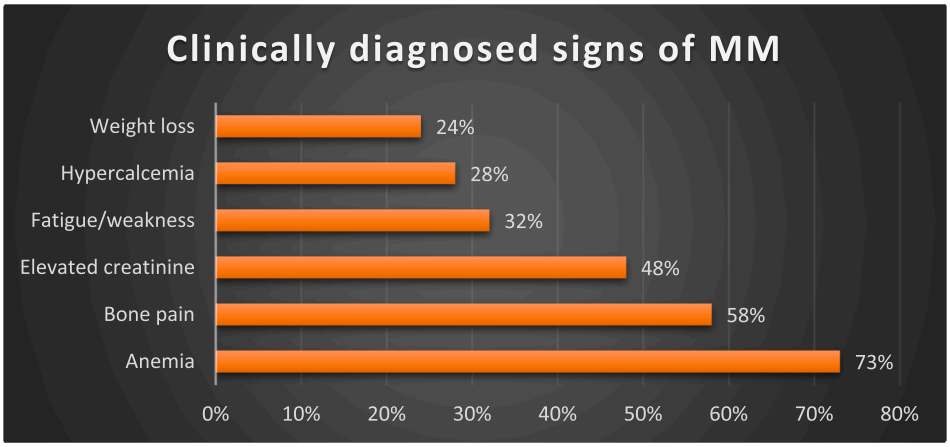

Fig. 5. Clinically diagnosed signs and symptoms of MM individuals (Tan et al., 2013).

Table 2
Multiple myeloma smouldering and non-secretory myeloma diagnosis, as well as multiple myeloma progression (Larsen et al., 2013; Schuster et al., 2010).

	M protein (g/dL)	Ig isotype	FLC ratio	Bone marrow plasma cell (%)	End-organ damage	Risk of MM progression
MGUS	≥1.5	Non-IgM	Abnormal	<10	Absence	kidney damage
	>1–3≤	IgM	Abnormal <100	<10	Absence	High-risk MM progression (osteolysis, kidney damage, anemia)
	<1.5	IgG	Normal ratio	<10	Absence	low risk MM progression
	Regardless of the type and amount of the M protein in the serum, <3	Light chain With no IgH	Abnormal high	<10	Absence	Light chain MM progression (bone pain and renal failure)
SMM	≥3	Non-IgM MGUS (IgG or IgA)	Abnormal	≥10-60≤	Absence	High-risk MM progression
	≥3	Light chain	Abnormal ≥100	≥10	Absence	High risk of MM progression
NSMM	Absence	Light chain	Abnormal	≥10	Positive	The risk of MM advancement is high (bone abnormalities, anemic conditions, metabolic alkalosis, and renal failure)

treatment. Patients with SMM have an increased risk of progression to symptomatic MM (Mina et al., 2023). The chance of developing a malignancy in the first five years after diagnosis, which is 10 % in SMM compared to 1 % in MGUS yearly, is the primary clinical difference between SMM and MGUS (Kyle et al., 2007). A subclass of patients with pre-cancerous signs, such as MGUS, and a portion of patients with biological malignancy, such as MM, who have not yet had hypercalcemia, renal failure, anemia, or bone abrasions are included in the clinically defined entity known as SMM. Biological heterogeneity (C; calcium; R; renal function tests, including urea and creatinine; A; anemia; B; bone diseases (CRAB)) and/or additional myeloma-defining events (MDE) are characteristics of SMM. As a result, people with SMM have a shallow rate of development and end-organ damage within the first two years after diagnosis, like people with MGUS (Rajkumar et al., 2012). To monitor the transition from SMM to MM, biomarkers such as MM defining events (MDEs) that recognize patients with an 80 % or higher chance of MM development are utilized. Light chain SMM is yet another subclass of SMM that can develop into MM. There is an excess of monoclonal FLC, and it has been noted that IgH is not expressed. Furthermore, IgH translocation, a type of genomic instability, was identical in SMM patients to both MGUS and active MM patients (Table 2) (Larsen et al., 2013). While there is a clinically recognized feature with biologic premalignancy like MGUS and biologic malignancy like MM, SMM is not a particular biologic stage in the progression from MGUS to MM (Dimopoulos et al., 2023).

5.3. Non-Secretory multiple myeloma (NSMM)

NSMM, or having no M proteins in the blood or urine, is only present in 3 % to 5 % of MM patients with neoplastic plasma cells producing an altered monoclonal component with a defect in serum and urine secretion of heavy and light chain (Table 2) (van de Donk et al., 2023). The FLC assay is beneficial for routinely tracking the response to therapy because it is aberrant in more than 60 % of patients. It has been found that M−protein is produced by plasma cells but cannot leave the cell and enter the extracellular space. Bone marrow contains just 10 % monoclonal plasma cells (Table 2) (Dutta et al., 2019). An immunofixation determines the absence of M−protein in the blood and urine protein determines the lack of M−protein in the blood determines the absence M−protein in the blood and urine protein determines the absence of M−protein in the blood and urine protein determines the absence of M−protein in the blood and urine protein determines the absence of M−protein in the blood and urine protein immunofixation assay determines the lack of M−protein in the blood and urine protein, which uses immunofluorescence, immune-peroxidase, and electrophoresis. With the FLC assay, the analysis of light chains only finds the light chain. As well as end-organ damage brought on by plasma cell proliferative disorders (CRAB), a lack of serum and urine monoclonal protein, and 10 % or more bone marrow plasma cell clones or by bone marrow biopsy, NSMM are described as these conditions mentioned in Table 2. Despite a large effector cell burden in the bone marrow and signs of organ malfunction, a deficiency in iNOS production produces no detectable protein in serum or urine (Dimopoulos et al., 2011). NSMM can be divided into four categories. The first group consists of MM with FLC restriction and FLC assay.

The second group, non-producers, is determined by intracellular immunofluorescence; MM is not secreted since no Ig is produced (monoclonal Ig detected in the cytoplasm). The third group, the Ig molecules, are produced by MM cells; however, they cannot be released into the extracellular area, making them true non-secretors. Finally, the fourth group contained the false non-secretors with immunofluorescence measurements of intracellular Ig in clonal plasma cells, and extracellular Ig was not detectable. For detecting lesions in NSMM patients, they use Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), which have a sensitivity of 90 % in patients with abnormalities detectable X-Ray, considered the gold standard. Several studies demonstrated the use of MRI and PET in NSMM patients because of the inability to use SPEP/UPEP/FLC tests due to limited response (Regelink et al., 2013).

5.4. Solitary plasmacytoma (SP)

Solitary plasmacytomas (SP), an unusual type of plasma cell dyscrasia, constitute 2–5 % of all plasma cell disorders (Grammatico et al., 2017). When bone lesions, anemia, renal disease, hypercalcemia, and/or renal insufficiency are present, the CRAB presentation can be distinguished from MM. Furthermore, a small percentage of plasma cell neoplasms (about 5 % to 6 %) can exhibit solitary plasmacytoma in bone or extramedullary tissues, which might assist in further distinguishing the CRAB presentation (Kilciksiz et al., 2012). It differs from MM by a constrained growth of malignant monoclonal plasma cells. The two kinds of SP are solitary extramedullary plasmacytoma (SEP) and solitary bone plasmacytoma (SBP), depending on whether the tumor appears in the bones or soft tissues (Dores et al., 2009). SBP occurs about 40 % more frequently than SEP does. The median age of SP patients at diagnosis is between 55 and 60 years old, which is lower than that in MM patients, and the ratio of male to female was found to range from 1:2:1 to 2:1 (Dimopoulos et al., 2011; Galieni et al., 2000). According to several studies, SP affects black people (30 %) more commonly than white people (Jawad & Scully, 2009). Pain, which can be brought on by bone loss, compression of the spinal cord and/or nerve roots, or compression and expansion of the affected soft tissue, is the most common sign and symptom that SP patients report.

5.5. Diagnosis sensitivity

Based on clinical diagnosis and routine blood testing after multiple myeloma is suspected, serum protein electrophoresis and serum free light chain assays detection of M protein and monoclonal excess of free light chains were set up. Serum protein electrophoresis will separate proteins based on size and charge and gives a quantitative measure of serum M protein, but it was considered an insensitive assay (Katzmann et al., 2009). In the interface of M protein's heavy and light chains, targeting hidden epitopes found in serum-free light chain assay can detect kappa and lambda-free light chains. This assay was not specific for monoclonal light chains, but monoclonality is observed if an abnormal kappa/lambda ratio and a ratio of <0.26 was obtained indicating a lambda clone and a ratio of >1.65 advocating a kappa clone (Katzmann et al., 2009). Kumar et al. observed that 20 % of multiple myeloma patients had only light chains,2 (Rajkumar & Kumar, 2016). To improve protein detection rates, it is necessary to perform serum-free light chain tests combined with serum protein electrophoresis methods (Table 3). Moreover, supplementary assay includes serum immunofixation electrophoresis, a qualitative assay that detects abnormal monoclonal proteins like IgA, IgM, IgG and light chain type (kappa or lambda) in serum. However, serum free light chain assay, protein electrophoresis method and immunofixation electrophoresis assay used in association increase the diagnostic sensitivity for MGUS by approximately 8 % and SMM by about 0,5 % (Katzmann et al., 2009).

In recent studies, it was observed that the use of mass spectrometry by the matrix-assisted laser desorptionionization–time of flight instruments (MALDI-TOF), is an assay using five separate Ig serum (IgG, IgA, IgM, Lambda and Kappa) that is considered as a fast and inexpensive method to detect monoclonal proteins (Katzmann et al., 2011). heavy and light chain enrichment after elution and reduction was observed in a stainless-steel plate with a laser format of five spots. The analysis of results was quickly obtained, and data was collected in 20 s in graph distribution (Barnidge et al., 2014). The IMWG updated the MM diagnostic guidelines in 2014; the new criteria consider key elements of MM therapy and are sufficient for MM diagnosis. Thus, the participant's diagnostic evaluation for suspected MM should include a complete blood count (CBC) with differential count, analysis of the serum chemistries, tests for lactate dehydrogenase, creatinine, 2-microglobulin, etc., immunoglobulin studies, whole-body CT or skeletal survey, and evaluation of the bone marrow. A significant number of malignant plasma cells that have differentiated from B cells is one of the key factors in diagnosing MM. Therefore, monoclonal immunoglobulins, cytokines, and chemokines are produced by cells that develop mainly in the bone marrow and are responsible for several clinical signs (Rajkumar, 2022). Advanced diagnostic criteria, including X-rays, MRIs, CT scans, and PET scans, are also used for diagnosis.

The International Myeloma Working Group (IMWG) has produced several MM diagnostic standards (Michels & Petersen, 2017). It is possible to observe the progression of MM after looking at proliferative malignant plasma cells in the bone marrow. These criteria comprise Table 4 summarizes the prognosis for MM, primary (premalignant stage) and secondary cytogenetic (malignant stage) abnormalities, hypercalcemia, renal insufficiency, anemia, and bone disease, as shown in Fig. 6. Additionally, they involve biopsy-confirmed bony or extramedullary plasmacytomas and more than 10 % of malignant plasma cells in the bone marrow (Michels & Petersen, 2017) (See Table 5.).

The clinical standards for the disease must be met to manage MM effectively. Over the most recent decades, the requirement was the existence of end-organ damage associated with CRAB and MDE. Three distinct biomarkers and well-established CRAB traits make up MDE (Gau et al., 2022):

1. The proliferative bone marrow has 60 % plasma cells.
2. A serum-free medium light chain (FLC) level of less than 100 mg/L.

Table 3
Diagnostic Sensitivity and specificity of Several Screening Methods Among 467 Patients with MM, 191 Patients with SMM, 524 Patients with MGUS and 29 Patients with SP (Katzmann et al., 2009).

Screening Test Methods	Diagnostic Sensitivity for MM n (%)	Diagnostic Sensitivity for SMM n (%)	Diagnostic Sensitivity for MGUS n (%)	Diagnostic Sensitivity for SP n (%)
SPEP alone	409 (87.6)	180 (94.2)	429 (81.9)	21 (72.4)
sIFE alone	441 (94.4)	188 (98.4)	486 (92.8)	21 (72.4)
sFLC alone	452 (96.8)	155 (81.2)	222 (42.4)	16 (55.2)
SPEP + sIFE + sFLC	467 (100)	191 (100)	509 (97.1)	26 (89.7)
SPEP + sFLC	467 (100)	190 (99.5)	465 (88.7)	25 (86.2)
SPEP + sIFE + uIFE	461 (98.7)	191 (100)	524 (100)	26 (89.7)
SPEP + sIFE + sFLC + uIFE	467 (100)	191 (100)	524 (100)	26 (89.7)

multiple myeloma (MM), single plasmacytoma (SP), monoclonal gammopathy of undetermined significance (MGUS), smouldering multiple myeloma (SMM), NSMM, serum protein electrophoresis (SPEP), serum and urine immunofixation electrophoresis (sIFE and uIFE), and quantitative serum free light chain (sFLC).

Table 4
Primary and secondary cytogenetic abnormalities, MM prognosis and progression (Barnidge et al., 2014).

Cytogenetic abnormality		Clinical Diagnosis	MM's prognosis and progression
Primary	Trisomies	- Myeloma bone disease at diagnosis	- Good prognoses - Standard-Risk MM
	t(11;14) (q13; q32)	- Cyclin D1 up-regulation - -Lymphoplasmacytic morphology - - Small serum monoclonal proteins	- Good prognoses - Standard-Risk MM
	t(6;14) (p21; q32)	- Cyclin D3 is up-regulated	- Good prognoses - Standard-Risk MM
	t(4;14) (p16; q32)	- Dysregulation of FGFR3 expression,	- High-Risk MM
	t(14;16) (q32; q23)	- High levels of FLC - Acute renal failure	- High-Risk MM
	t(14;20) (q32; q11)	- Aberrant expression of MAFB	- Poor diagnosis - High-risk MM
Secondary	Gain(1q21)	- Increases copy number of cyclin kinase subunit 1B (CKS1B) gene - Lower IgM - Higher platelet count	- High-risk MM
	Del(17p)	- Loss of TP53 function	- High-risk MM
	Trisomies + one of IgH translocations	- Myeloma bone disease at diagnosis. - Clinical diagnosis corresponding to translocation	- High-risk MM
	- Isolated monosomy 13 - Isolated monosomy 14	**Monosomy 13:** - History of MGUS - Correlated with MGUS to MM progression **Monosomy 14:** - Lack of IgH translocations and trisomies	- Effect on prognosis is not clear

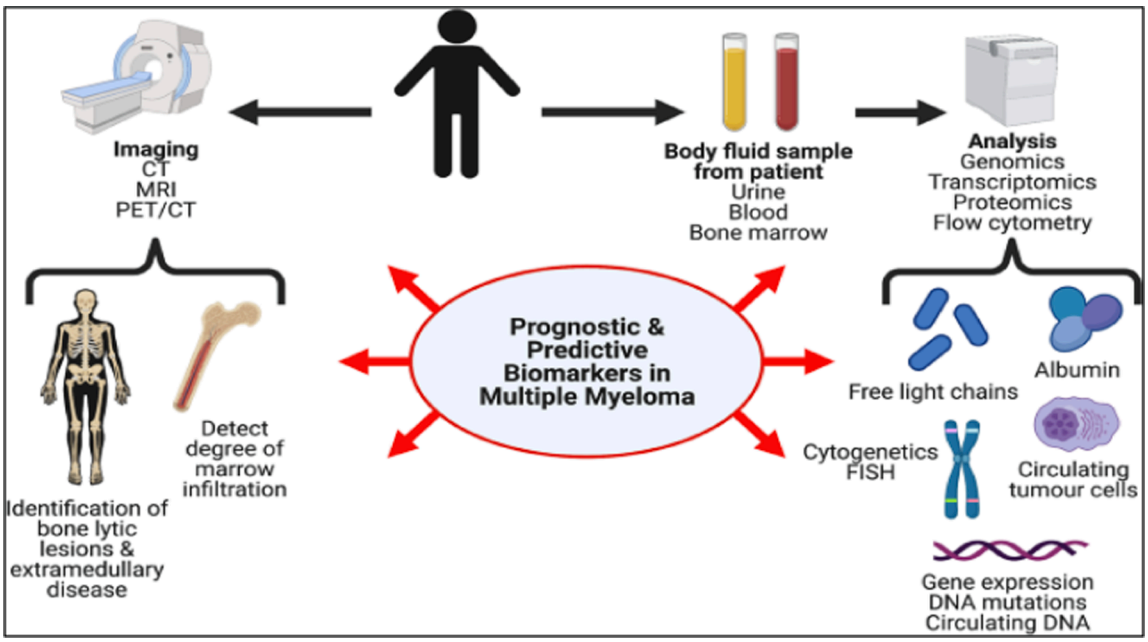

Fig. 6. Developments of diagnostic and predictive biomarkers in multiple myelomas (Rajkumar & Kumar, 2016).

Table 5
Clinical values due to end-organ damage in multiple myeloma.

Calcium threshold	Serum calcium >0.25 mmol/L (>1 mg/dL) Serum calcium >2.75 mmol/L (>11 mg/dL)
Kidney damage	Creatinine clearance of less than 40 mL per minute Serum creatinine > 177 mol/L (> 2 mg/dL)
Anemic condition	Hemoglobin levels less than 100 g/L

3. Several localized lesions on MRI, PET, and CT.

The criteria determining MM's development were modified in 2019, allowing for improved patient care, particularly for those with greater risk of disease development, enabling earlier therapy, and preventing catastrophic organ damage. These criteria were changed by the IMWG and given the designation " IMWG criteria connected with the traditional CRAB criteria" (Rajan & Rajkumar, 2015; Tan et al., 2013). According to the literature, revised MM can be diagnosed without CRAB criteria if one of these indicators, IMWG, is present. According to the latest research, these markers have been linked to more than 80 % of the possibility of experiencing organ damage. The modified IMWG guidelines for detecting MM include extramedullary plasmacytoma, proliferative bone marrow malignant plasma cells >10 %, bone marrow biopsy, one or more CRAB criteria, and MDE (Eisfeld et al., 2023). Due to the nature of the plasma cell proliferating problem, end-organ damage may occur in the following nature of the plasma cell proliferating problem. End-organ damage may occur in the conditions mentioned in Table 4. Osteolytic lesions on skeletal radiography, CT, PET, or MRI are among the bone lesions. A serum intricate/uncomplicated FLC proportion of 100 with a concentration of engrossed FLC 100 mg/l was used to distinguish between SMM and MM requiring therapy. Several focal lesions on MRI are ≥5 mm in size (Durie et al., 2020).

6. Clinical analysis for the characterization of MGUS, SMM, and NSMM

The following should be included in the analysis to characterize the MGUS, SMM, and NSMM and to diagnose MM progression in patients.

6.1. Blood tests

Complete blood counts, immunofixation electrophoresis, serum protein electrophoresis, and FLC assays are all necessary blood tests. Platelets, leukocytes, and erythrocytes can also be counted. The objective is to quantify the degree of interference with MM with normal blood cell development. Low red blood cell counts can signify anemia, a greater risk of infection, and a weakening of the blood clotting process. To assess the activity of the renal, hepatic, and bone tissues as well as the severity of the disease, the blood sample's chemistry, which includes albumin, calcium, LDH, blood urea nitrogen (BUN), and creatinine, can be examined. These tests could be referred to as CRAB tests. Aberrant levels indicate that the bone, liver, or kidney functions are abnormal, indicating the severity of the MM condition. It is also possible to determine the level of ß2-microglobulin (ß2-M), a protein that helps with disease staging, by indicating the frequency and severity of MM and kidney function. The magnitude of the MM disease's proliferative potential is marked by higher levels (Rajkumar & Kumar, 2016). It is also possible to determine the quantity and kind of antibodies (IgM, IgG, or IgA) present in the blood to determine whether myeloma cells are overproducing IgG or IgA antibodies. A serum protein electrophoresis blood test can also be carried out to ascertain the presence and concentration of the many proteins that make up the monoclonal (M protein) created by myeloma cells.

A technology named immunological electrophoresis, sometimes referred to as immunofixation electrophoresis (IFE), aids in the staging or classification of MM disease by identifying the kind of abnormal antibody proteins that are present in the blood. The FreeliteTM serum-free light chain test can also be used to determine how many antibodies light chains (kappa or lambda) myeloma cells produce unusually high or low levels of kappa, lambda, or both proteins can be used to indicate myeloma (Lin, 2009).

Leuco-erythroblastosis and the proliferation of red cell rouleaux in peripheral smears are also significantly prognostic of MM. Therefore, even if the illness may be intermittent, a bone marrow sample is required to show and assess whether aberrant malignant plasma cells are present in the bone marrow. The trephine sample, however, sometimes provides a more precise result. Myeloma cells are typically observed in the cell trails of the hypercellular bone marrow fragments. The percentage of monoclonal plasma cells in the general population can also be measured

using bone marrow immunohistochemistry and flow cytometry (Lin, 2009).

6.2. Urine test

A Urine test should be conducted, including a Urine test with protein quantification and Immuno-fixation electrophoresis. Screening of urine is another diagnostic method. Urine analysis testing is the initial step in evaluating kidney function. Abnormal results may reveal renal failure. It is possible to quantify the occurrence and content of Bence Jones proteins by analyzing a 24-hour urine sample. A urine protein electrophoresis test can further confirm the presence and amounts of proteins in the urine (Greipp et al., 2005).

6.3. Bone marrow biopsy

To assess variations and malformations in the bone structure and to ascertain the number and mass of bone tumors, comprehensive examinations should be carried out using techniques like bone (skeletal) surveys, X-rays, MRI, CT-scan, and PET, as well as cytology, histopathology, and flow cytometry. Symptoms of MM include an abnormally high degree of bone variation. Biopsies can be done on either bone tissue or bone marrow fluid to determine the quantity and proportion of abnormal and normal malignant plasma cells in the bone marrow (Greipp et al., 2005). To determine the presence of mutations, cytogenetic procedures such as karyotyping and FISH can be used to determine the number and existence of chromosomes.

6.4. Clinical analysis of different stages of MM and their survival rates

The proportion of ß2-M in the serum, the concentration of LDH, and specific gene abnormalities (cytogenetics) of the developed tumor have all been used to grade MM by using the Revised International Staging System (RISS) mentioned in Table 6 (Greipp et al., 2005). However, cancer staging can be a challenging endeavour. Survival rates are commonly calculated by previously reported results of numerous MM patients. The percentage of patients with similar types and stages of cancer who survive for a predetermined amount of time (usually five years) after a patient's survival rate indicates diagnosis. Generally, 5-year survival rates are widely used in statistics to describe the prognosis for a particular kind of cancer. The reality of any one patient's illness cannot, however, be predicted by mortality rates. MGUS and SMM are distinguished in the literature based on an arbitrary laboratory procedure. Using current clinical knowledge is limited since some patients with MGUS can quickly, even if they seem to have a small ailment consignment, and many patients with SMM will persist even if they are categorized as having a higher disease burden of MGUS (Lakshman et al., 2018; Landgren et al., 2019).

Table 6
The Revised International Staging System (3 stages) in Multiple Myeloma (Durie et al., 2020).

RISS	VALUES Sβ2M	MM progression	Survival rates (RISS Median Survival)
I	- Sβ2M<3.5 mg/l - Alb≥3.5 g/dl - Standard-risk chromosomal abnormalities by FISH - - Normal LDH	**Standard risk myeloma** - Single plasmacytoma - Focal lesion - - Limited disease	Has not been reached
II	- Not R-ISS stage I or III	**Intermediate risk myeloma** - Translocation t(4;14)	83 months
III	- Sβ2M≥5.5 mg/L - High-risk Chromosomal abnormalities by FISH - - High LDH	**High-risk myeloma** *(one or more of the following)* - Del(17p) - t(14;16) or t(14;20) in the IgH - Plasma cell leukemia - Increasing level of lactate dehydrogenase - High-risk signature on gene expression profiling studies	43 months

New technology, such as next-generation sequencing (NGS), has enabled more complete genetic investigations in patients in the last decade, and this has played a vital role therapeutically in providing replicable alternatives to MM disease. Several studies have shown that genetic events are crucial in determining the stage of MM development (Bolli et al., 2020). The limited knowledge in the clinic is a consequence of the technical limitations, such as the small number of bone marrow plasma cell clones, which limits the ability to conduct sequencing assays, necessitating investigations on SMM patients rather than MGUS patients. Studies conducted in 2021 promoted the development of novel clinical analyses based on modern technology to understand better and identify myeloma precursors. The analysis is based on multiparametric bone marrow plasma cell flow-sorting using a flow cytometry cell sorter and low-input whole-genome sequencing (WGS) technology. This allows for avoiding difficulties associated with clonal plasma cell volume and contamination by normal plasma cells. Furthermore, this innovative technique enabled researchers to investigate MGUS, SMM, and MM (M. Dimopoulos et al., 2009; Grammatico et al., 2017).

Mono variants, structural variants, gene mutation hallmarks, and nucleotide sequence variants can all be found using WGS in MGUS and SMM patients who are both clinically stable and progressing. The best understanding will allow us to differentiate between progressive and stable myeloma precursors in patients using technologies like FISH, single-nucleotide polymorphism arrays (SNPA), and gene expression technologies that show the presence of genomic aberrations on chromosomes and expression signatures, given the shorter time to MM progression. Predicting the course of the myeloma precursor is critical (Bruno et al., 2016; Lee-Six et al., 2019; Rajkumar & Kumar, 2016; van Rhee et al., 2014). Finally, to improve medical support and treatment methods, genetic aberrations must be identified to detect individuals with progressive myeloma precursors before clonal proliferation, end-organ destruction, and significant clinical problems and to improve patient follow-up (Kyle et al., 2018).

7. Treatment of MM

One of MM's most successful novel progressive cures is monoclonal antibodies (mAbs), which include PIs and IMiDs. MM standard of living and overall median survival rates have significantly improved, and some patients have experienced long-term survival following auxiliary treatment for bone disease. So, f-year survival has increased from an estimated 30 % in 1990 to about 45 % in 2007 (Bianchi & Anderson, 2014). The recommended treatment strategy for MM involves stem cell grafting and two or three drugs of myeloablative chemotherapy (ASCT). Some studies have found a 10 % long-term survival rate, and ASCT increases the median survival of MM patients by roughly a year (Rajkumar & Kumar, 2016; van Rhee et al., 2014). Most of the time, people over 65 and those with long-term disabilities have not been denied access to this treatment but have instead received unconventional chemotherapy. Since age alone does not prevent benefit from this treatment, the more precise therapies are now accessible to healthy older individuals (Bruno et al., 2016). It has been demonstrated that the presumption that older patients would be in good physical condition, weak, or in between is a predictor of therapy interruption and overall survival (Palumbo et al., 2015). Usually, induction chemotherapy is administered to potential

ASCT candidates before transplantation.

Treatment for patients with severe renal injuries must concentrate on the causes. For instance, 3L per day of intravenously normal saline is advised for kidney dysfunction (Bird et al., 2011). To lower the light chain load, dexamethasone is frequently given with chemotherapy to patients with renal impairment and noticeably increased blood light chain levels (S. K. Kumar et al., 2018). However, it is advised against giving toxic medications to MM patients and conducting contrast-enhanced imaging tests (145). The IMWG summary report on managing MM-related bone disease advocated intravenous zoledronic acid or pamidronate for all MM patients, regardless of bone metastases (Kumar et al., 2018). In one randomized control study, zoledronic acid boosts survival rates, even though both bisphosphonates have been shown to reduce spinal compression fractures and other bone issues (Dimopoulos et al., 2009; Mhaskar et al., 2012). A RANKL inhibitor, XGEVA (denosumab), is also approved for treating cancer patients with BMs or MM to prevent skeletal-related issues (Cadieux et al., 2022).

Additionally, calcium and vitamin D3 supplements should be regularly taken by MM patients, with caution, when calcium is administered to those who have renal issues. While spinal cord compression that has already occurred or is about to occur should be treated by an orthopaedic or neurosurgery specialist, balloon kyphoplasty is effective for MM patients who have experienced a vertebral compression fracture (Terpos et al., 2013).

Additionally, severe infections are a significant danger for MM patients, making prompt detection and treatment essential. A fluoroquinolone or trimethoprim/sulfamethoxazole for the first 12 weeks of treatment are two examples of situations where prophylactic antibiotics are advised (Palumbo et al., 2015; Rajkumar et al., 2014). However, preventive penicillin prescriptions are only intended for recurrent, severe bacterial infections, not persistent pneumococcal infections. In contrast, intravenous immunoglobulin is prescribed for these illnesses. The American Society of Clinical Oncology (ASCO) advises using low molecular weight heparin or warfarin for four to six months during the first diagnosis period or until the disease is under control to prevent thromboembolic events, which are very pervasive in MM patients, especially those who are receiving immunomodulatory therapies (Falanga et al., 2012). Based on prognostic variables, patients are classified as having conventional or high-risk MM:

- Lenalidomide-low dosage dexamethasone (Rd) or bortezomib-cyclophosphamide dexamethasone (VCD) are used to treat patients with high-risk diseases (Durie et al., 2017).
- Patients who meet the criteria for transplantation may undergo ASCT after four months of therapy. If the initial ASCT did not produce a satisfactory response, a second ASCT may be considered. In such cases, patients may receive reduced doses of chemotherapy if the transplant is postponed until the disease's progression is stopped (Al Hamed et al., 2019).
- Alkylating drugs, anthracyclines, corticosteroids, thalidomide, lenalidomide, bortezomib, and other therapies for relapsing disease were used alone or in combination.

7.1. Systemic treatment

7.1.1. Radiotherapy

This is an illustration of primary treatment, specifically targeting cells in a constrained area of the body, specifically targeting cells in a constrained body area. In MM patients, radiation therapy is most frequently utilized to treat painful plasmacytoma or achy bone deterioration. Only radiotherapy can cure a single plasmacytoma, a mass of malignant cells (Terpos et al., 2013). Increased radioactivity harms the tumour's genes or halts the growth of new cancer cells. The most common form of radiation therapy is external beam radiation therapy (EBRT), used to treat solitary plasmacytoma. Radiation therapy, however, can have adverse side effects that may become apparent after a few sessions, including uncomfortable, hazardous, or emotional issues. Other signs and symptoms include exhaustion, which may worsen with nausea, diarrhoea, a lack of appetite, weight loss, and hair loss (Barlogie et al., 1987).

7.1.2. Surgical interventions

This entails a procedure to eradicate or restor a body portion. Solitary plasmacytomas outside of the bone can be removed with local surgery, often used when radiation therapy is not an option. However, a bone fracture brought on by MM may be repaired surgically. However, radiation therapy can also be given before or following surgery. Despite this, patients may still develop an infection, oedema, post-operative pain, and exhaustion (Barlogie et al., 1987).

7.1.3. Specifically targeted medication

This pharmacological therapy specifically targets a characteristic of cancer cells, making it unlikely that healthy cells will suffer side effects. As angiogenesis inhibitors, several medications used in targeted therapy prevent the creation of more blood veins that fuel the propagation of myeloid cells in the bone tissues. Other related drugs serve as protein inhibitors (PIs) by preventing the action of specific protein families, such as proteasomes, which support the survival of myeloma cells (Bruins et al., 2020). Cell death is brought on by a replacement group that prevents the histone deacetylase enzymes from performing their activity (HDAC inhibitors). Another targeted therapy that binds to proteins in cancer cells is monoclonal antibodies or synthetic antibodies like Daratumumab. PIs include Ixazomib, Carfilzomib, and Bortezomib, among others. Panobinostat is an illustration of an HDAC inhibitor. Conditions that are undesirable or unhealthy on a physical or mental level are among the downsides of targeted therapy (Bruins et al., 2020).

7.1.4. Chemotherapy

In this instance, drugs are utilized to eradicate cancer cells. Depending on the regimen, it is administered in cycles of 14–21–28 days of treatment, with days in between to allow the body to recover. Corticosteroids, a prototype of dexamethasone, methylprednisolone, and prednisone, are used in clinical medicine for induction and other treatments. It is rarely used except for spinal cord compression, acute renal injury caused by light chains, and hypercalcemia (high calcium levels). Water retention, immunological suppression, lack of sleep, mood swings, and gastrointestinal toxicity are some of its adverse effects, though hyperglycemia. Apart from spinal cord compression, acute renal injury caused by light chains, and elevated calcium levels, it is seldom implemented separately. However, some of its negative consequences include hydration, immunosuppression, gastrointestinal toxicity, and unusually high blood sugar levels (Bianchi & Anderson, 2014). For inducement, integration, and relapse, IMiD combinations like thalidomide and lenalidomide (Revlimid) are successful. The drawbacks include increased thrombotic risk, myelosuppression, peripheral neuropathy, sleepiness, bradycardia, constipation, and somnolence. Other IMiDs like pomalidomide are also FDA-approved and can potentially change patient outcomes, in addition to belantamab (ADC/BCMA) and BCMA CAR-T cell (Idea-Cel, Cilta-Cel). For the therapy of MM, research is being done on the BCMA protein's targeting of plasma cells. During the technique, antibody-drug conjugates, chimeric antigen receptors (CAR), and antibody-drug conjugates can mobilize immune system cells to kill myeloma cells (Lassiter et al., 2021). Clinical combinations of carfilzomib (Kyprolis) and bortezomib (Velcade) can treat relapse, consolidation, and cancer induction. They cannot be utilized alone, however. Peripheral and autonomic neuropathy, thrombocytopenia, and varicella-zoster virus reactivation are typical adverse effects (Roy et al., 2015). However, due to the chance of varicella-zoster virus reactivation, preventive antiviral medication is advised for MM patients taking PIs. Exhaustion, low blood cell counts, abdominal discomfort, incontinence, bacterial infection or mouth sores, lack of appetite

(anorexia), hair loss (alopecia), and loss of appetite are possible side effects of chemotherapy (Bird et al., 2011).

7.1.5. Steroids

A class of medication used to treat swelling and inflammation is steroids. Dexamethasone, a steroid, has anti-cancer properties (Gau et al., 2022). Some of the side effects of these steroids include increased body weight, an increased risk of infection, mood swings, and osteoporosis, as well as irritability and anxiousness, along with appetite, sleepiness, slow wound healing, incontinence, swelling and oedema in the ankles and hands (Gau et al., 2022).

7.1.6. Proteasome inhibitors (PIs) in myeloma bone disease

For the treatment of MM, PIs are observed as an essential therapeutic approach (Okazuka & Ishida, 2018). Over the past few decades, many creative PIs have dramatically improved MM patient care and survival. The lowering of RANKL-mediated osteoclast differentiation is controlled by PIs, which regulate bone metabolism (Terpos et al., 2007). By binding RANKL to RANK on the surface of osteoclast precursors and promoting NF-kB activation, PIs can restrict osteoclast genesis and reduce bone resorption by blocking this pathway. Furthermore, PIs obstruct the ubiquitin-protease pathway, which supports bone resorption (Qiang et al., 2012). Researchers are now looking at multiple medications and varieties, including Venetoclax (Venclexta, Venclyxto). Leukemia and lymphoma can be effectively treated with BCL-2 inhibitors. Additionally, it might help treat myeloma cases with a genetic mutation that affects 20 % of cases of the disease (Blair, 2020). In recent studies, venetoclax has demonstrated promising activity, notably in the t(11;14) patient population and in patients with degenerated or intractable MM who had taken many treatments (Sidiqi et al., 2021). Myeloid cell malignancy 1 (Mcl-1) overexpression has been connected to MM's poor prognosis and therapy resistance. Overexpression of Bcl-2 family proteins has been shown to alter the pathogenesis of MM. The Mcl-1 protein has been proposed to be inhibited from killing myeloma cells. The drug class is being developed to treat myeloma cells (Sidiqi et al., 2021). Several combination formulae are also being studied to determine their effectiveness at thwarting MM. These combinations consist of bortezomib and lenalidomide in addition to dexamethasone, bortezomib, cyclophosphamide, dexamethasone, carfilzomib, lenalidomide, dexamethasone, and ixazomib, lenalidomide (Al-Odat et al., 2021; Gerecke et al., 2016; Larocca et al., 2017).

7.1.7. Stem cell transplant

This involves substituting unhealthy bone stem cells for functioning bone marrow cells to repair the bone marrow. Chemotherapy suppresses the bone marrow before transplanting healthy blood stem cells. To produce the desired outcome, these cells develop into fresh bone marrow and blood cells (Roy et al., 2015). The two primary procedures for stem cell transplantation are allogenic transplantation, which uses blood stem cells from a donor, and autologous transplantation, which utilizes a patient's blood to restore or rejuvenate bone marrow after a heavy chemotherapy regimen. Tandem, micro, and donor lymphocyte infusion are a few more cell transplant procedures. A physical or mental condition brought on by a stem cell transplant is unpleasant or unhealthy (Mhaskar et al., 2012).

7.1.8. Drawbacks of contemporary drug therapies for MM

New interventional therapy has been developed as the incidence and death of MM rise. Target drug therapies (IMiDs, PIs, mAbs), transplantation of stem cells combination therapies (based on lenalidomide or bortezomib), bisphosphonate therapy, corticosteroids, and radiation therapy are a few of these. Immunomodulatory drugs (IMiDs), which regulate the immune system by altering T cell activity and cytokine production, represent the most recent advancements in novel targeted pharmacological therapy.These drugs induce apoptosis by interfering with these immune system balancing mechanisms. Since it was initially made available as an IMiD in 1999, thalidomide has been the subject of extensive in vitro and clinical phase II research, assessing both its effectiveness when used alone and when coupled with other medications like dexamethasone.However, the initial side effects of thalidomide, including myasthenia (muscle weakness), faintness, sleepiness, and constipation, limit its efficacy). Proteasomes regulate regulatory proteins to preserve cellular homeostasis. The medicine bortezomib, studied in stages I–III throughout the previous year, is a member of the first generation of PIs. On the other hand, the grade III side effects of bortezomib have been linked to thrombocytopenia, exhaustion, and neuropathic pain (Richardson et al., 2007). To change growth rates or trigger death, monoclonal antibodies, a new family of protein treatments first nicknamed "magic bullets," impede ligand binding and signalling. Daratumumab, a human CD38 monoclonal antibody that damages cells related to MM, is the most well-known medication for treating MM (Adams & Weiner, 2005). The immediate side effects of monoclonal antibodies have also been linked to cardiovascular events, cytokine release syndrome, and antigenic responses such as acute anaphylaxis and serum sickness (Corren et al., 2009; De Weers et al., 2011).

8. Recommendations for the management of MM

According to the Joint Clinical Practice Guideline of the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO), the following are the guidelines for the management of MM (Mikhael et al., 2019).

8.1. Applicable transplantation

The criteria used to determine a patient's eligibility for an autologous stem cell transplant (ASCT), the options for pre-transplant therapy, the recommendation for post-transplant treatment, and the realistic response goals for transplant-eligible patients are all included in the guidelines for the population that is qualified for transplant surgery (Mohty & Harousseau, 2014). The parameters of recommendations for the transplant-appropriate population include the following subjects: standards for determining a case suitability for an autologous stem-cell transplant (ASCT); choices for pre-transplant therapies; suggested post-transplant medicines; and the realistic response targets for transplant-suitable cases (Devarakonda et al., 2021). The experts offered several recommendations based on the evidence, the quality of the evidence, the benefits versus the dangers, and the recommendations' strength. MM patients must first go to a transplant facility to find out if they are candidates for transplant. Age and renal function should not be the primary factors determining Stem Cell Transplant (SCT) eligibility (De Weers et al., 2011). The ideal treatment strategy and the ideal number of cycles are yet uncertain. Before SCT, it is recommended to administer immunomodulatory drugs, PIs, and steroids in addition to at least three to four series of induction therapy (Jayaweera et al., 2021; Kumar et al., 2014). However, this is not always feasible. All eligible patients should have the option of receiving an immediate transplant. The recommended course of action is to refrain from administering drugs linked to stem-cell toxicity, such as melphalan and/or long-term (four cycles) immunomodulatory drug exposure, to patients who are strong candidates for SCT (Poczta et al., 2021). However, continuing with long-term therapy may reduce the number of stem cells that can be extracted. The minimal response level necessary to move on to SCT for individuals receiving induction treatment is not acknowledged. However, regardless of how much of a reaction the patients receive, they should be advised to have SCT (Papy-Garcia & Albanese, 2017).

Melphalan is advised as a conditioning method for ASCT at a high dosage. Combination ASCT shouldn't be regularly recommended, although salvage or delayed SCT can be used as a support or stabilization for individuals who initially decline the transplant operation at the first sign of relapse. Even though allogeneic transplants and consolidation

therapy are not usually advised for the treatment of MM, they may be taken into consideration for a small number of highly high-risk patients or in a clinical trial setting. If you are not a transplant candidate or are afraid to begin maintenance therapy, consider consolidation therapy for at least two cycles. Depending on the treatment results, standard-risk patients should typically start taking lenalidomide maintenance medicine at 10–15 mg daily for about three to four months. Because maintenance therapy for at least 24 months is connected to improved survival, it is encouraged to try to continue treatment for at least two years. Additionally, people who cannot take lenalidomide because of physical restrictions should consider taking bortezomib maintenance every 14 days. High-risk patients may also be candidates for therapy with a PI that contains or does not contain lenalidomide (Merz et al., 2020).

The present data do not provide enough support for changing maintenance therapy based on the degree of response and minimal residual disease (MRD) occurrence (Kostopoulos et al., 2020). The best depth of remission should be the target of the first therapy for transplant candidates. Although MRD negative status is linked to better or improved outcomes, it shouldn't be utilized to track treatment goals unless it's part of a clinical study (Charalampous & Kourelis, 2022). An assessment of the response's depth should be a part of every cycle. After achieving the desired response, the assessment or maintenance therapy should be given no less frequently than once every 12 weeks. It has been demonstrated that low-dose whole-body CT- scans are superior to conventional X-rays for skeletal assessment (Jayaweera et al., 2021). The most effective method for initial and ongoing bone surveillance is a CT scan. At baseline and in certain circumstances, fluorodeoxyglucose PET/CT can be used alternately with MRI (Chrzan et al., 2017).

8.2. Precluded transplantation

Here, guidelines for primary therapy should be made based on agreements between patients and physicians for MM patients who are unfit for transplant (Derudas et al., 2020). The disease's chromosomal abnormalities and stage, as well as patient-specific characteristics such as comorbidities, age, disability status, health status, and patient preferences, must be considered (Derudas et al., 2020; Kumar, 2011). A new treatment (IMiD or PI), ideally a steroid, should be explored as part of the initial course of therapy for MM patients who are unsuitable for transplantation. There should also be consideration given to triple therapy, such as daratumumab, bortezomib, melphalan, and prednisone, or bortezomib, lenalidomide, and dexamethasone. The degree and length of treatment should be adjusted based on the quality-of-life assessment (symptom management and treatment tolerance) to determine whether the therapy goals are being maintained and met (Poczta et al., 2021). The treatment goals might need to be adjusted based on how the patient responds, their symptoms, and their quality of life. Additionally, it is indicated that patients should be closely monitored with dose adjustments to changes in fever or infection levels, liver and renal function, toxicity, neutropenia, performance status, and side effect tolerance (Merz et al., 2020).

8.3. Relapsed MM

According to the study, the treatment of individuals who have relapsed disease should be customized based on the patient's response to previous medication, the frequency of myeloma signs, cytogenetic risk, the existence of comorbidities (such as renal failure), infirmity, and disposition (Mikhael et al., 2019). Genetic predisposition or high-risk patients should receive the proper care only once, as shown by high-risk cytogenetics and early post-transplant/preliminary therapy recurrence (Dingli et al., 2017). Patients with MM who are relapsing gradually and asymptomatically should be under close supervision. It is crucial to start treating all clinically relapsed MM patients right away. On the initial relapse, triple therapy should be administered, but the patient's tolerance for more significant toxicity needs to be considered. Two unique agents are included in a triplet regimen. Without disease remission, treatment for relapsed MM may continue (Wallington-Beddoe et al., 2018). However, the suggestion of a risk-based vs a response-based treatment duration is not backed by enough evidence, e.g., MRD. Previous therapies should be considered when selecting a course of treatment for a first recurrence. Consider combining a monoclonal antibody-based therapy with an IMiD and/or PIs (Gandhi et al., 2019). Triplet regimens are the best since they address the issues with tolerability and comorbidities. If ASCT is not part of initial induction therapy, patients eligible for transplants with relapsed MM should have it. They must also be free of MM. If the transformation lifespan achieved after the initial transplant was 18 months or longer, repeat SCT may be considered in cases of recurrent MM (Antoine-Pepeljugoski & Braunstein, 2019). The use of conventional chemotherapy regimens, nuclear export-blocking medications, CAR-T and NK cell therapies, next-generation monoclonal antibodies, and bispecific antibodies has recently been investigated. It has shown promise in clinical investigations for treating triple-refractory MM (Stalker & Mark, 2022). If the new drugs are insufficient, patients with relapsed and refractory myeloma can get salvage chemotherapy. Whether dexamethasone was given with thalidomide, cisplatin, doxorubicin, cyclophosphamide, or etoposide, about 50 % of patients who got it in clinical studies reacted. Other varieties utilized in conventional therapy include high-dose cyclophos, dexamethasone, thalidomide, cisplatin, doxorubicin, and etoposide (Gerrie et al., 2013; Ronchetti et al., 2013).

Research is being done on Melphalan fulafenamide melflufen, a peptide pharmaceutical molecule, as a potential novel treatment for triple-refractory MM. Melflufen releases an alkylating moiety into MM cells by utilizing their elevated aminopeptidase activity compared to non-malignant cells (Gandhi et al., 2019). Melphalan flufenamide was considered a potential treatment for triple-class refractory MM in the HORIZON and O-12-M1 studies. Patients who experienced a complete response in the phase II HORIZON study in RRMM had an objective response rate (ORR) of 29 %, whereas those with the triple-refractory disease had an ORR of 26 %. PFS, OS, and response time were 4.2, 11.6, and 5.5 months each (Miettinen et al., 2021; Richardson et al., 2021; Tabchi et al., 2019).

Venetoclax, a brand-new medication with an innovative action method, has shown promising results in RRMM, especially in situations of high BCL-2 activity brought on by t(11; 14) mutations (Richardson et al., 2019b). In the randomized phase III trial (BELLINI), which compared venetoclax-bortezomib-dexamethasone with bortezomib-dexamethasone, venetoclax had a higher ORR, 82 % compared to 69 %. The PFS was also longer in the venetoclax arm, coming in at 22.4 months as opposed to 11.5 months. Stalker and his associates conduct in-depth reviews of all novel drugs for treating Triple-Class RMM (S. K. Kumar et al., 2020). However, it has been approved that ciltacel treatment is associated with an increased response rate and superior PFS and OS compared to standard treatment for patients with RRMM who have not responded to therapy with IMID, PIs, and anti-CD38 MoAb. The anti-BCMA CAR-T cell therapy ciltacabtagene autoleucel (ciltacel; JNJ-68284528), which has been demonstrated to be effective in treating RRMM patients who were resistant to both IMiD and PIs or who had received at least three prior lines of therapy and had been exposed to anti-CD83, is the subject of the single-arm study CARTITUDE-1 (Tabchi et al., 2019). According to a survey, 95 matchings were made between the 69 mITT patients (54 of whom received bridging therapy), the ITT patients (75 of whom received bridging therapy and 82 of whom received ciltacel), and the MAMMOTH patients. Pomalidomide was the next drug administered to 34 % of patients in the MAMMTH ITT cohort, followed by anti-CD38 MoAb (24 %), carfilzomib (19 %), and cytotoxic chemotherapy (35 %). The ORR for CARTITUDE-1 was more significant in the ITT cohorts (84 % vs. 28 %). Patients in the CARTITUDE-1 ITT cohort had higher 12-month PFS and 12-month OS rates than those in the MAMMOTH cohort. CARTITUDE-1 patients surpassed other mITT

cohorts in terms of ORR (96 % vs. 30 %), PFS (12 mo. 79 % vs. 15 %), and OS (12 mo. 88 % vs. 41 %) (Nikonova et al., 2016).

In SWOG S0777, a randomized phase III trial (bortezomib, lenalidomide, and dexamethasone -VRD) and (lenalidomide and dexamethasone -Rd) were assessed. All patients received an initial 6-month induction phase of eight 21-day VRD cycles and six 28-day Rd cycles, then Rd management with an average follow-up of 84 months. The median progression-free survival for each was 41 months, the pooled hazard ratio (96 % Wald Confidence Interval) for VRD and Rd was 0.742, the one-sided pooled log-rank P-value for each was 0.003, and so on (0.594, 0.928). The stratified two-sided P-value was 0.0114, and the segregated relative risk (96 % Wald Confidence Interval) was 0.709. (0.543, 0.926). While the median survival for VRD has not yet been attained, it is 69 months for Rd. As a result of the VRD versus Rd age adjustment, PFS and OS both rose (P-values: 0.013 for PFS and 0.033 for OS). RD maintenance lasted 17.1 months on average. Both statistical validity and diagnostic accuracy are shown when bortezomib is delivered along with lenalidomide and dexamethasone as part of the induction treatment. Regardless of age, VRD continues to offer a satisfactory grade of care (Rajkumar, 2022).

In the single-arm, phase 1b/2 CARTITUDE-1 study, it was discovered that the CARTITUDE-1 vs. MAMMOTH ITT cohorts had better overall response rates (ORR; 84 % vs. 28 % [P.001]), longer progression-free survival (PFS; hazard ratio [HR], 0.11 [95 % confidence interval (CI), 0.05–0.22]), and longer overall survival (OS; HR, 0.11). Similar results were observed using different matching procedures in mITT cohorts of CARTITUDE-1 vs MAMMOTH (ORR: 96 % vs 30 % [P.001]; PFS: HR, 0.02 [95 % CI, 0.01–0.14]; OS: HR, 0.05 [95 % CI, 0.01–0.22]) (Costa et al., 2022).

For people with RRMM, researchers are constantly hunting for a safe drug that works well and has few side effects. As a result, several drugs have entered phase III trials; some have proved effective, while others might be discontinued for a few different reasons.

In clinical studies where the inclusion criteria included refractoriness and/or at least past therapy with lenalidomide, pomalidomide has been demonstrated to have exceptional benefits when paired with other drugs. Phase II RCTs showed that PCd appears to be working well and that OS was improved when dexamethasone was combined with pomalidomide and cyclophosphamide (PCd) as contrasted to dexamethasone alone (Pd) (median PFS: 9.5 months) (Miettinen et al., 2021; Richardson et al., 2021). In phase III research, it was discovered that Pd with isatuximab led to better outcomes than Pd alone, although a higher prevalence of multiple grades 3–4 side effects resulted in associated discontinuations. In contrast, phase 1b research on 103 patients who had undergone extensive therapy discovered that the combination of daratumumab (DPd) was effective (ORR of 60 %, median PFS of 8.8 months, and median OS of 17.5 months) (Chari et al., 2017; Richardson et al., 2019a).

Pomalidomide, bortezomib, and dexamethasone (the triplet PVd) outperformed Vd in terms of efficacy in a group of patients whose 100 % had taken lenalidomide and 71 % had had unsatisfactory responses to therapy (Richardson et al., 2019b).

Finally, two phases 3 RCTs have been completed to determine whether combining Pd with nivolumab with or without elotuzumab (CheckMate-602; ClinicalTrials.gov number, NCT02726581) or with belantamab mandolin is efficacious (DREAMM8; ClinicalTrials.gov number, NCT04484623) (Richardson et al., 2019b).

Additionally, consideration should be given to other risk variables such as age, extramedullary illness, renal insufficiency, the incidence of plasma cell leukemia/circulating plasma cells, and fragility (Hernández-Rivas et al., 2022). For patients with inherited high-risk diseases, the initial course of treatment should consist of a triplet of PIs, immunomodulatory medicines, and steroids, followed by one or two ASCTs, and then PIs-based maintenance until the course of treatment has advanced (Boyiadzis et al., 2016). Drugs should be modified for renal clearance in patients with renal impairment. Cytotoxic therapy may also be essential for patients with plasma cell leukemia or extramedullary illness (Boyiadzis et al., 2016). The IMWG updated response criteria should be used to gauge how well patients are responding to therapy. All quantifiable standards, including the studies of the light and heavy chains, must be strictly followed (Costa et al., 2021). The IMWG criteria should be used to validate each response, excluding bone marrow and imaging. After one round of therapy, a response evaluation should be done. The assessment may be performed every other cycle if a response trend is discovered and less frequently when the patient reaches peak response (Costa et al., 2022).

9. Conclusions and future perspectives

With the development of novel IMiDs and PIs and the longer survival of newly diagnosed patients, active treatment should continue until symptoms and/or end-organ damage become obvious or impending. Further research is needed to determine each patient's specific combination and delivery order of these cutting-edge therapy regimens. Several studies aimed to better understand the determinants of antibody drug conjugation (ADC) internalization in multiple myeloma cells to determine ADC sensitivity and resistance to adjust the treatment.

Immunotherapies, including autologous CAR T-cell-based therapies and bispecific antibodies, are drawing considerable attention among others. However, we are still quite behind in understanding MM's heterogeneous biology and therapeutic implications. Therefore, we need to elucidate further the efficacy of new agents, especially in combinatory treatments with forthcoming treatment modalities such as immunotherapies with CAR T cells and bispecific antibodies, to make the best use of these essential agents and obtain better and more beneficial therapeutic outcomes in patients with MM. Allogeneic CAR T-cell therapy overcomes the limitations of conventional autologous CAR T-cells.

Examining the bone marrow environment is vital for diagnosing MGUS and MM, and it has also influenced the appearance of these two diagnostic features (Capp & Bataille, 2018). Additionally, the early recognition of clonal events and potential targets is considered one of the most promising future directions for the early detection of MM progression. Decorin plays a crucial role in the interaction of proteins between osteoblasts and plasma cells in the endosteal niche (Capp & Bataille, 2018). Then, by examining Decorins expression dysregulation or osteoblasts, we can gain a better knowledge of the role of the bone marrow in MGUS and MM-causing frequencies (Capp & Bataille, 2018; Wallington-Beddoe & Mynott, 2021).

This unique target for effective therapy necessitates epigenetic and phenotypic study. Although epigenetic interventions can induce such normalization of cell morphologies, their efficacy has yet to be proven. Several studies on multiple myeloma have reported the necessity of inducing the expression of repressed genes to find a dynamic arrangement of the biological system in the bone marrow to stimulate the stimulation of osteoblast proliferation and survival. Moreover, several studies show that chromosomal abnormalities in bone progenitor dysfunction characterize some acute myeloid leukemia. Numerous research on MM have indicated the need to increase the expression of suppressed genes to identify a dynamical arrangement of the biological system in the bone marrow to promote the stimulation of osteoblast proliferation and survival. Consequently, it would be interesting to test the beneficial effects of some drugs that can modulate the bone marrow environment on the precursor cells of MM and, more precisely, drugs that can stimulate bone formation in osteoporosis and MGUS patients (Capp & Bataille, 2018). Thus, MGUS could be considered a pre-MM state identified by clonal chromosomal markers in bone marrow progenitor dysfunction—furthermore, the potential for personalized treatments or gene knockdown to limit the progression of MM in treatment.

Funding

The Deanship of Scientific Research (DSR) at King Abdulaziz University (KAU), Jeddah, Saudi Arabia has funded this project, under grant no. (RG-5-140-43).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors gratefully acknowledge technical and financial support from the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, Saudi Arabia.

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