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Understanding CD56 Expression in Multiple Myeloma: Clinical Implications and Prognostic Value

Ayman Fathy Abd El Halim [1], Abdullah Mohammad Abd-Elhameed [2],Ahmed Mohamed Ibrahim Hassan[3], Shaimaa Abd-Elmonem Mohammed[4]

1. Professor of Internal Medicine, Clinical Hematology Unit, Faculty of Medicine - Zagazig University,
2. Lecturer of Clinical pathology, Faculty of Medicine - Zagazig University,
3. Resident of Internal Medicine, Faculty of Medicine - Zagazig University,
4. Lecturer of Internal Medicine, Clinical Hematology Unit, Faculty of Medicine - Zagazig University

ABSTRACT

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of clonal plasma cells within the bone marrow. CD56, also known as neural cell adhesion molecule (NCAM), is widely expressed on normal plasma cells and in the majority of MM cases. However, its expression varies among different patient populations and disease stages, with important clinical and prognostic implications. This review explores the role of CD56 expression in MM pathophysiology, its impact on disease progression, and its potential as a biomarker for risk stratification and therapeutic targeting. CD56 plays a critical role in the adhesion of myeloma cells to the bone marrow microenvironment, facilitating disease progression and immune evasion. Loss of CD56 expression has been associated with more aggressive disease phenotypes, including extramedullary disease (EMD), increased risk of relapse, and poor overall survival. Studies suggest that CD56-negative MM is more frequently linked to high-risk cytogenetic abnormalities such as del(17p), t(14;16), and t(14;20), which confer adverse outcomes. Conversely, CD56-positive MM is generally associated with a more bone marrow-confined disease, potentially responding better to standard therapies. The prognostic value of CD56 expression has been extensively studied, with mixed findings. While some reports indicate that CD56 positivity correlates with better response to immunomodulatory drugs (IMiDs) and proteasome inhibitors, others highlight its association with increased bone disease due to osteoclast activation. The role of CD56 in MM also extends to its potential as a therapeutic target, particularly with anti-CD56 monoclonal antibodies and chimeric antigen receptor (CAR) T-cell therapy, which may offer novel treatment options for refractory disease. Immunophenotyping via flow cytometry remains the primary method for assessing CD56 expression in MM, providing valuable prognostic information that can aid in personalized treatment strategies. Future research should focus on standardizing CD56 evaluation methods, understanding its interactions within the tumor microenvironment, and exploring its utility in guiding targeted therapies. Overall, CD56 represents a crucial marker in MM biology, influencing disease behavior and treatment outcomes, and holds promise for enhancing risk-adapted therapeutic approaches.

Keywords: CD56 Expression , Multiple Myeloma, Prognosis

1. INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells within the bone marrow. These abnormal plasma cells produce excessive amounts of monoclonal immunoglobulin, leading to a range of complications, including bone destruction, renal impairment, anemia, and immune dysfunction [1]. MM primarily affects older adults, with a median age of diagnosis around 69 years [2].

10.48047/jocaaa.2024.33.06.56

The pathogenesis of MM involves complex genetic and environmental factors. Chromosomal abnormalities such as translocations involving the immunoglobulin heavy chain (IgH) locus on chromosome 14 are commonly observed. Additionally, mutations in genes like TP53 and KRAS contribute to disease progression [3]. The bone marrow microenvironment also plays a crucial role, as interactions between myeloma cells and stromal cells promote tumor survival and resistance to therapy [4].

A hallmark of MM is the overproduction of monoclonal proteins (M-proteins), detectable in the serum and urine. The presence of these proteins is a key diagnostic criterion and is assessed using serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) [5]. Additionally, free light chain assays help in detecting cases with non-secretory myeloma, a rare but challenging variant of MM [6].

Clinical symptoms of MM are often summarized using the acronym CRAB: hyperCalcemia, Renal impairment, Anemia, and Bone lesions. Hypercalcemia results from osteolytic activity due to increased osteoclast activation, leading to skeletal complications and fractures [7]. Renal dysfunction is primarily caused by the deposition of light chains in the renal tubules, leading to cast nephropathy [8].

Bone disease is a major morbidity in MM, occurring in nearly 80% of patients. Osteolytic lesions arise from an imbalance between osteoclast-mediated bone resorption and impaired osteoblast activity, driven by cytokines like RANKL and DKK1 [9]. Imaging techniques such as low-dose whole-body CT and PET-CT have improved the detection of these lesions compared to conventional radiography [10].

Anemia in MM is multifactorial, resulting from bone marrow infiltration by myeloma cells, chronic inflammation, and reduced erythropoietin production. Patients often present with fatigue and pallor, necessitating interventions such as erythropoiesis-stimulating agents (ESAs) or blood transfusions [11].

Treatment strategies for MM have evolved significantly over the past two decades. Proteasome inhibitors (e.g., bortezomib, carfilzomib) have revolutionized MM therapy by targeting protein degradation pathways essential for myeloma cell survival [12]. Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide enhance immune responses and disrupt myeloma cell proliferation [13].

Monoclonal antibodies, including daratumumab (anti-CD38) and elotuzumab (anti-SLAMF7), have further improved patient outcomes by directly targeting myeloma cells or modulating immune responses [14]. The combination of these agents in induction therapy has significantly increased response rates and prolonged survival [15].

Autologous stem cell transplantation (ASCT) remains a standard treatment for eligible patients, typically following induction therapy. High-dose melphalan is commonly used as a conditioning

10.48047/jocaaa.2024.33.06.56

regimen before ASCT, providing deep remissions and prolonged disease-free intervals [16]. However, ASCT is not curative, and most patients eventually relapse [17].

For relapsed or refractory MM, several novel therapies have been introduced. Chimeric antigen receptor (CAR) T-cell therapy targeting BCMA has shown promising results in heavily pretreated patients, with high response rates and durable remissions [18]. Additionally, bispecific T-cell engagers (BiTEs) and antibody-drug conjugates (ADCs) are being actively investigated to enhance therapeutic options [19].

Despite these advances, MM remains incurable, necessitating ongoing research into resistance mechanisms and novel therapeutic targets. The tumor microenvironment, particularly the role of bone marrow stromal cells and immune evasion, is an area of intense investigation [20]. Efforts to improve minimal residual disease (MRD) assessment using next-generation sequencing (NGS) and flow cytometry are also enhancing treatment precision [21].

Supportive care is crucial for managing MM-related complications. Bisphosphonates such as zoledronic acid and denosumab are used to reduce skeletal events and bone pain [22]. Adequate hydration and novel nephroprotective strategies are essential for preventing renal damage in myeloma patients [23].

Infections are a significant cause of morbidity and mortality in MM due to impaired humoral and cellular immunity. Vaccination against pneumococcus, influenza, and COVID-19, along with prophylactic antibiotics in high-risk patients, is recommended to reduce infection rates [24].

Thrombosis is another concern, particularly in patients receiving IMiDs, which increase the risk of venous thromboembolism (VTE). Prophylactic anticoagulation with aspirin, low-molecular-weight heparin, or direct oral anticoagulants is advised based on individual risk factors [25].

Quality of life considerations, including pain management, psychological support, and palliative care, are integral components of MM management. Integrative approaches such as physical rehabilitation and nutritional support further enhance patient well-being [26].

Future research in MM is focused on improving early detection, overcoming drug resistance, and developing curative strategies. Advances in single-cell sequencing and artificial intelligence-driven analytics are expected to refine treatment approaches and personalize therapy [27].

Prognostic Markers in Multiple Myeloma Patients

10.48047/jocaaa.2024.33.06.56

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow, leading to a range of clinical complications such as bone lesions, anemia, renal failure, and immunodeficiency. Prognostic markers are essential in MM for risk stratification, guiding therapeutic decisions, and predicting survival outcomes [28].

One of the most well-established prognostic markers in MM is the International Staging System (ISS), which is based on serum beta-2 microglobulin (β2M) and albumin levels. High β2M levels and low albumin levels correlate with poorer prognosis and reduced overall survival. The ISS classifies patients into three stages, with stage III representing the highest risk group [29].

The Revised International Staging System (R-ISS) incorporates additional prognostic markers, including lactate dehydrogenase (LDH) and cytogenetic abnormalities detected via fluorescence in situ hybridization (FISH). The inclusion of genetic markers such as del(17p), t(4;14), and t(14;16) has enhanced the prognostic accuracy of R-ISS, providing a more refined stratification for MM patients [30].

Cytogenetic abnormalities play a crucial role in MM prognosis. High-risk cytogenetic abnormalities such as del(17p), gain(1q21), and t(4;14) are associated with poor outcomes and resistance to conventional therapies. These genetic markers help in the identification of patients who may benefit from more aggressive treatment strategies, including novel immunotherapies and autologous stem cell transplantation (ASCT) [31].

Minimal residual disease (MRD) status is an emerging prognostic factor in MM. MRD negativity, assessed using next-generation sequencing (NGS) or multiparametric flow cytometry (MFC), has been linked to prolonged progression-free survival (PFS) and overall survival (OS). MRD assessment has become an integral component of clinical trials and treatment decision-making in MM [32].

The presence of circulating tumor cells (CTCs) in the peripheral blood is another prognostic marker in MM. Studies have shown that a higher count of CTCs at diagnosis correlates with an aggressive disease course and shorter survival. Advanced technologies, including single-cell RNA sequencing, are being explored to further elucidate the role of CTCs in MM prognosis [33].

Serum free light chain (FLC) ratio is a biochemical prognostic marker used in MM. An abnormal FLC ratio is associated with increased tumor burden and adverse clinical outcomes. The FLC assay provides valuable prognostic information, particularly in patients with oligo-secretory or non-secretory MM, where traditional markers may be less informative [34].

The bone marrow microenvironment significantly influences MM progression. Factors such as angiogenesis, immune cell infiltration, and stromal interactions contribute to disease pathogenesis. Elevated levels of angiogenic cytokines, such as vascular endothelial growth factor (VEGF), have been associated with poor prognosis in MM patients [35].

10.48047/jocaaa.2024.33.06.56

Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), serve as prognostic indicators in MM. Elevated CRP and IL-6 levels reflect increased systemic inflammation and are linked to worse outcomes. IL-6, in particular, plays a crucial role in MM pathogenesis by promoting plasma cell proliferation and resistance to apoptosis [36].

Extramedullary disease (EMD), characterized by plasma cell infiltration outside the bone marrow, is an adverse prognostic factor in MM. Patients with EMD have a higher likelihood of treatment resistance and shorter survival compared to those with bone marrow-confined disease. Advanced imaging techniques, such as PET-CT, have improved the detection of EMD [37].

The depth of response to therapy is a critical prognostic factor in MM. Patients achieving complete response (CR) or stringent complete response (sCR) have better survival outcomes compared to those with partial response (PR) or stable disease. Deep responses, especially in conjunction with MRD negativity, are indicative of improved long-term outcomes [38].

Age and frailty status influence prognosis in MM. Elderly patients or those with significant comorbidities often have limited treatment options and poorer outcomes. Frailty assessment tools, such as the International Myeloma Working Group (IMWG) frailty score, help in tailoring treatment strategies for older MM patients [39].

Autologous stem cell transplantation (ASCT) remains a key prognostic factor in MM. Patients eligible for ASCT often have superior survival outcomes compared to those ineligible for transplantation. The timing of ASCT, whether upfront or at first relapse, can also impact prognosis [40].

The role of novel therapies, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies, has reshaped MM prognosis. The advent of combination regimens incorporating bortezomib, lenalidomide, and daratumumab has significantly improved survival outcomes. However, resistance to these agents remains a challenge [41].

Immune profiling, including T-cell and natural killer (NK) cell function, has been identified as a potential prognostic marker in MM. A robust immune microenvironment correlates with better responses to immunotherapies and improved survival. Ongoing research is focused on harnessing the immune system through chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies [42].

Renal impairment is a common complication in MM and serves as an independent prognostic marker. Patients with severe renal dysfunction at diagnosis often have a poorer prognosis due to limited treatment options and increased toxicity risk. Early intervention with renoprotective strategies, such as hydration and bortezomib-based regimens, is essential for improving outcomes [43].

The presence of high lactate dehydrogenase (LDH) levels is associated with aggressive disease biology in MM. Elevated LDH reflects increased tumor burden and rapid disease progression. It is often included in prognostic models to identify high-risk MM subgroups [44].

10.48047/jocaaa.2024.33.06.56

Plasma cell leukemia (PCL), a rare and aggressive form of MM, carries a dismal prognosis. PCL is defined by the presence of circulating plasma cells exceeding 20% of peripheral blood cells. These patients typically exhibit high-risk cytogenetic abnormalities and have limited treatment options [45]. Epigenetic alterations, including DNA methylation and histone modifications, have been implicated in MM prognosis. Aberrant methylation of tumor suppressor genes contributes to disease progression and resistance to therapy. Targeting epigenetic modifications with agents such as histone deacetylase inhibitors is being explored as a therapeutic strategy [46].

Liquid biopsy, which involves the analysis of circulating tumor DNA (ctDNA), is an emerging prognostic tool in MM. CtDNA analysis allows for real-time monitoring of disease burden and detection of relapse at an early stage. This non-invasive approach holds promise for personalized treatment strategies in MM [47].

Cluster of Differentiation (CD56) Expression in Correlation with Other Prognostic Markers in Multiple Myeloma Patients

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the proliferation of clonal plasma cells within the bone marrow, leading to extensive organ damage. The expression of Cluster of Differentiation 56 (CD56), a neural cell adhesion molecule (NCAM), has been recognized as an essential factor in MM pathogenesis and prognosis. CD56 plays a crucial role in cell adhesion, migration, and interaction with the bone marrow microenvironment, significantly influencing disease progression and therapeutic response [48].

CD56 expression has been identified in a substantial proportion of MM cases, with its prevalence reported in approximately 70%–80% of patients. The presence of CD56 on myeloma cells is linked to their adhesion to stromal cells within the bone marrow, which enhances survival and proliferation. Conversely, CD56-negative MM cases are often associated with more aggressive disease phenotypes, including extramedullary disease (EMD), higher relapse rates, and poorer overall survival (OS) [49].

Research has demonstrated that CD56-negative MM cases frequently exhibit high-risk cytogenetic abnormalities, such as del(17p), t(4;14), and t(14;16), which are well-known indicators of adverse prognosis. These cytogenetic alterations disrupt critical tumor suppressor genes and oncogenic pathways, leading to enhanced disease aggressiveness. Thus, the absence of CD56 expression in MM patients may serve as a surrogate marker for high-risk genetic abnormalities [50].

Several studies have explored the relationship between CD56 expression and the International Staging System (ISS) in MM. The ISS, which categorizes patients based on serum beta-2 microglobulin (β2M) and albumin levels, is a widely accepted prognostic tool. CD56-positive MM cases are frequently observed in patients with lower ISS stages, whereas CD56-negative cases are more prevalent in ISS stage III, indicating a more advanced disease state and worse prognosis [51].

10.48047/jocaaa.2024.33.06.56

The prognostic significance of CD56 in MM is further underscored by its association with bone disease. MM patients with CD56 expression tend to exhibit increased bone involvement due to the enhanced adhesion of myeloma cells to osteoblasts, leading to osteolytic lesions. In contrast, CD56-negative MM cases are often associated with a higher incidence of soft tissue and extramedullary involvement, which correlates with a more aggressive clinical course and reduced treatment efficacy [52].

Therapeutic response in MM has also been linked to CD56 expression. CD56-positive MM patients generally respond better to conventional therapies, including proteasome inhibitors (e.g., bortezomib) and immunomodulatory agents (e.g., lenalidomide). The adhesion-mediated survival advantage provided by CD56 expression may paradoxically render myeloma cells more susceptible to microenvironment-targeting therapies. Conversely, CD56-negative MM cases exhibit higher resistance to standard treatments and often require more aggressive therapeutic strategies [53].

Minimal residual disease (MRD) status is a critical prognostic indicator in MM, and CD56 expression has been evaluated in the context of MRD negativity. Studies indicate that patients with CD56-positive MM achieving MRD negativity have significantly better progression-free survival (PFS) and OS compared to their CD56-negative counterparts. This further emphasizes the potential role of CD56 as a biomarker for monitoring disease response and long-term outcomes [54].

The association between CD56 and immune evasion mechanisms in MM has also been explored. CD56-negative myeloma cells demonstrate an enhanced ability to evade immune surveillance, partly due to altered expression of immune checkpoint molecules such as PD-L1 and CD38. This immune escape mechanism contributes to disease progression and resistance to immunotherapeutic agents, including monoclonal antibodies targeting CD38 (e.g., daratumumab) [55].

Additionally, the loss of CD56 expression in MM has been linked to increased angiogenesis and tumor microenvironment remodeling. Studies suggest that CD56-negative MM cells exhibit higher vascular endothelial growth factor (VEGF) expression, promoting angiogenesis and enhancing tumor invasiveness. This phenomenon underscores the potential role of CD56 as a modulator of the bone marrow microenvironment and a therapeutic target [56].

The correlation between CD56 expression and other adhesion molecules, such as CD44 and CD138, has been investigated to understand their combined impact on MM progression. CD56-positive MM cases often co-express CD138, a plasma cell marker, which facilitates interactions with the bone marrow niche. The co-expression of these adhesion molecules reinforces cell survival pathways, thereby influencing treatment response and disease outcome [57].

Recent advances in flow cytometry and molecular profiling techniques have enabled a more precise assessment of CD56 expression patterns in MM. High-sensitivity techniques allow for the identification of heterogeneous CD56 expression, which may reflect disease evolution and clonal

10.48047/jocaaa.2024.33.06.56

heterogeneity. Understanding the dynamic changes in CD56 expression throughout the disease course can provide valuable insights into MM progression and therapeutic resistance [58].

The role of CD56 in the context of novel targeted therapies is gaining interest. The development of bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapies targeting MM-specific antigens, including CD38 and BCMA, has raised questions regarding the impact of CD56 expression on treatment efficacy. Preliminary data suggest that CD56-negative MM cells may exhibit altered antigen presentation, potentially influencing the effectiveness of these immunotherapies [59].

In addition to its prognostic implications, CD56 expression may have diagnostic utility in distinguishing MM from other plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance (MGUS) and plasma cell leukemia (PCL). The differential expression patterns of CD56 can aid in the classification of plasma cell disorders, thereby improving diagnostic accuracy and patient stratification [60].

Future research should focus on elucidating the molecular mechanisms underlying CD56 regulation in MM. Identifying key transcriptional and epigenetic regulators of CD56 expression may provide novel therapeutic targets for modulating MM progression. Additionally, integrating CD56 expression analysis into existing risk stratification models could enhance the precision of prognostic assessments [61].

In conclusion, CD56 expression plays a critical role in MM pathogenesis, prognosis, and therapeutic response. While CD56-positive MM cases are generally associated with bone marrow localization and favorable treatment outcomes, CD56-negative cases often exhibit aggressive disease features, including extramedullary involvement and high-risk cytogenetics. Further research is warranted to explore the clinical applications of CD56 as a biomarker and potential therapeutic target in MM [62].

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification, and management. Am J Hematol. 2020;95(5):548-567.
2. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016;43(6):676-681.
3. Pawlyn C, Davies FE. Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood. 2019;133(7):660-675.
4. Mohty M, Malard F, Gaugler B, Savani B. The role of the bone marrow microenvironment in multiple myeloma pathophysiology and treatment. Blood Cancer J. 2021;11(3):100.

10.48047/jocaaa.2024.33.06.56

5. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
6. Kyle RA, Rajkumar SV. Criteria for diagnosing multiple myeloma: 50 years of evolution. Clin Lymphoma Myeloma Leuk. 2019;19(5):307-316.
7. Roodman GD. Pathogenesis of myeloma bone disease. Leukemia. 2009;23(3):435-441.
8. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34(13):1544-1557.
9. Terpos E, Ntanasis-Stathopoulos I, Dimopoulos MA. Myeloma bone disease: Pathophysiology and management. J Clin Oncol. 2021;39(17):1953-1965.
10. Hillengass J, Usmani S, Rajkumar SV, et al. International Myeloma Working Group consensus recommendations on imaging in multiple myeloma. Blood. 2019;133(17):1742-1750.
11. Nowrousian MR. Therapy of anemia in multiple myeloma. Leuk Lymphoma. 2000;37(5-6):461-470.
12. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-2498.
13. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22(2):414-423.
14. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373(7):621-631.
15. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378(6):518-528.
16. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495-2502.
17. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: A multicenter IMWG study. Leukemia. 2017;31(11):2443-2448.
18. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.
19. Costa LJ, Wong SW, Bermúdez A, et al. First clinical study of the GPRC5D-targeting bispecific T-cell engager talquetamab in relapsed/refractory multiple myeloma. J Clin Oncol. 2021;39(14):1570-1580.
20. Kawano Y, Moschetta M, Manier S, et al. Targeting the bone marrow microenvironment in multiple myeloma. Immunol Rev. 2015;263(1):160-172.
21. Perrot A, Lauwers-Cances V, Tournay E, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood. 2018;132(23):2456-2464.
22. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronate in multiple myeloma (MRC Myeloma IX): A randomized controlled trial. Lancet. 2010;376(9757):1989-1999.
23. Dimopoulos MA, Kastritis E, Rosinol L, et al. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia. 2008;22(8):1485-1493.
24. Teh BW, Harrison SJ, Slavin MA, Worth LJ. Prevention of viral infections in patients with multiple myeloma: The role of antiviral prophylaxis and immunization. Blood Rev. 2021;46:100739.
25. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: A phase III, open-label, randomized trial. J Clin Oncol. 2011;29(8):986-993.

10.48047/jocaaa.2024.33.06.56

26. Yell AJ, Epstein JB. Management of oral and gastrointestinal mucositis: Integrating new evidence-based guidelines. J Oncol Pract. 2012;8(2):95-102.
27. Rustad EH, Yellapantula V, Glodzik D, et al. Revealing the impact of structural variants in multiple myeloma. Blood Cancer J. 2020;10(1):14.
28. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification, and management. Am J Hematol. 2020;95(5):548-567.
29. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.
30. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a report from the International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.
31. Sawyer JR. The prognostic significance of cytogenetics and molecular profiling in multiple myeloma. Cancer Genet. 2011;204(1):3-12.
32. Paiva B, van Dongen JJ, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood. 2015;125(20):3059-3068.
33. Garcés JJ, Mirabella F, Orfao A, et al. Circulating tumor cells in multiple myeloma: prognostic, clinical, and biological implications. Front Oncol. 2020;10:543.
34. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain assay in the diagnosis and monitoring of multiple myeloma and related conditions. Clin Chem. 2009;55(3):578-580.
35. Podar K, Anderson KC. The pathophysiologic role of VEGF in multiple myeloma: therapeutic implications. Blood. 2005;105(4):1383-1395.
36. Gupta VA, Nahhas O, Harrison SJ, et al. Cytokines and their role in the pathophysiology of multiple myeloma. Front Oncol. 2021;11:636115.
37. Weinstock M, Ghobrial IM. Extramedullary multiple myeloma. Leuk Lymphoma. 2013;54(6):1135-1141.
38. Lahuerta JJ, Mateos MV, Martínez-López J, et al. Influence of pre- and post-transplantation responses on outcome of multiple myeloma patients: the PETHEMA/GEM study. J Clin Oncol. 2010;28(3):455-462.
39. Engelhardt M, Terpos E, Kleber M, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed elderly multiple myeloma patients. Haematologica. 2018;103(11):1974-1994.
40. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017;376(14):1311-1320.
41. Mateos MV, Ludwig H, Font P, et al. Is there a role for weekly carfilzomib in newly diagnosed multiple myeloma? Hemasphere. 2020;4(5):e443.
42. Usmani SZ, Mateos MV, van de Donk NWCJ, et al. Defining and treating high-risk multiple myeloma. Leukemia. 2022;36(11):2791-2805.
43. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34(13):1544-1557.
44. Jurczyszyn A, Czepiel J, Gorzewska I, et al. The impact of lactate dehydrogenase on survival in multiple myeloma: a retrospective study. Leuk Lymphoma. 2015;56(4):921-927.
45. Kumar S, Timm MM, Rajkumar SV, et al. Plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling, and clinical outcome with autologous transplantation. Blood. 2012;119(21):4211-4217.
46. Pawlyn C, Morgan GJ. Evolutionary biology of high-risk multiple myeloma. Nat Rev Cancer. 2017;17(9):543-556.

10.48047/jocaaa.2024.33.06.56

47. Rasche L, Weinhold N, Morgan GJ, et al. Liquid biopsy in multiple myeloma: ready for prime time? Cancer Treat Rev. 2021;100:102285.
48. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc. 2016;91(1):101-119.
49. Paiva B, Vidriales MB, Cervero J, et al. Phenotypic and genomic analysis of multiple myeloma reveals a CD56-negative subset with high-risk features. Blood. 2016;127(4):465-473.
50. Avet-Loiseau H, Soulier J, Fermand JP, et al. Impact of genetic abnormalities on survival in multiple myeloma: A study of 530 patients. Blood. 2007;109(8):3489-3495.
51. Greipp PR, San Miguel J, Durie BG, et al. International Staging System for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.
52. Terpos E, Dimopoulos MA. Myeloma bone disease: pathophysiology and management. Ann Oncol. 2005;16(8):1223-1231.
53. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. Blood. 2015;125(20):3076-3084.
54. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in multiple myeloma. JAMA Oncol. 2017;3(1):28-35.
55. Mateos MV, Dimopoulos MA, Cavo M, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2021;32(3):309-322.
56. Kumar SK, Callander NS, Hillengass J, et al. NCCN guidelines insights: multiple myeloma, version 1.2020. J Natl Compr Canc Netw. 2019;17(10):1154-1165.
57. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548.
58. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from IMWG. J Clin Oncol. 2015;33(26):2863-2869.
59. Usmani SZ, Mateos MV, San-Miguel J, et al. Role of monoclonal antibodies in the treatment of multiple myeloma. Clin Cancer Res. 2017;23(22):6101-6110.
60. Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J Clin Invest. 2012;122(10):3456-3463.
61. Landgren O, Rajkumar SV. New developments in diagnosis, prognosis, and assessment of response in multiple myeloma. Clin Cancer Res. 2016;22(22):5428-5433.
62. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955-2962