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RESEARCH PROGRESS IN THE DIAGNOSIS AND TREATMENT OF MULTIPLE MYELOMA

YiFan Ding[1], Hu Xiao[2*]
[1]*School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China.*
[2]*Department of Clinical Laboratory, Fengxian Central Hospital, Shanghai 201499, China.*
[*]*Corresponding Author: Hu Xiao*

Abstract: Multiple myeloma (MM) is a hematologic disorder characterized by clonal abnormal proliferation of malignant plasma cells in the bone marrow, accompanied by the presence of monoclonal immunoglobulins or their fragments in the blood and urine. The most important tools for diagnosing MM include molecular diagnosis, bone marrow cytology, and imaging, etc. The early symptoms of MM are atypical and easily misdiagnosed or missed, and need to be combined with several laboratory tests to make a comprehensive judgment. In recent years, research on oncogenesis, cytogenetics and molecular biology has been fruitful, and a variety of biomarkers such as microRNA, circulating tumor cells, circulating free DNA, circulating tumor DNA, etc. have been found to be related to multiple myeloma, which can be used for the auxiliary diagnosis of MM, predicting disease progression or for subsequent therapeutic targets. And with the development of science and technology, artificial intelligence and machine learning can also assist physicians in analysis and diagnosis. Meanwhile, monoclonal antibody therapies, targeting B-cell maturation antigens, etc. have also been shown to have better clinical efficacy in the treatment of multiple myeloma. The purpose of this article is to review the laboratory tests that are important for the diagnosis of multiple myeloma and the treatment options for the disease, to provide a basis and direction for the clinical diagnosis and treatment of multiple myeloma, and to improve the detection rate and efficacy of multiple myeloma.
Keywords: Multiple myeloma; Diagnosis; Treatment

1 INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy characterized by the abnormal clonal proliferation of plasma cells. It is hallmarked by the accumulation of a massive number of malignant plasma cells within the bone marrow, leading to the invasion of the bone marrow and other organs or tissues. Although its incidence rate is relatively low, the threat it poses cannot be overlooked [1]. Statistics indicate that the average survival time of untreated MM patients is merely 3-5 years, whereas the median survival can be extended to 7-10 years for those receiving treatment. Consequently, the diagnosis and treatment of MM have emerged as focal points of current research.

In terms of MM diagnosis, imaging examinations remain one of the most commonly utilized modalities. Modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) can detect skeletal lesions and plasmacytoma foci, facilitating the early detection of MM. Furthermore, hematological, immunological, and endocrinological evaluations serve as standard adjunctive diagnostic tools. A pivotal hematological test is the detection of monoclonal immunoglobulins, also known as M-proteins. The M-protein is an immunoglobulin produced by the abnormal proliferation of plasma cells in MM patients, and its presence serves as a critical diagnostic indicator. Moreover, biomarkers play a crucial role in MM diagnosis. Frequently utilized biomarkers include serum β2-microglobulin, serum free light chain (FLC) ratio (κ/λ), and urine Bence Jones protein (BJP). These biomarkers provide supplementary information that aids in assessing disease progression and prognosis [2]. With the advancement of scientific research, emerging biomarkers, such as microRNAs (miRNAs) and circulating tumor cells (CTCs), have garnered increasing attention. These novel biomarkers hold the promise of providing more accurate and comprehensive information for the diagnosis, prognostic evaluation, and therapeutic monitoring of MM.

Regarding the therapeutic landscape of MM, despite significant advancements, several challenges persist. Firstly, MM patients frequently present with concomitant organ damage, complicating surgical interventions. Secondly, the substantial adverse effects associated with chemotherapy and immunotherapy significantly impact patients' overall health and quality of life. Furthermore, consolidation and maintenance therapies remain imperative for patients experiencing relapse or metastasis to enhance therapeutic efficacy. As medical technology continues to evolve, our understanding of MM deepens, imposing higher demands on its diagnosis and management. This article aims to provide a comprehensive review of the recent research progress in the diagnosis and treatment of multiple myeloma.

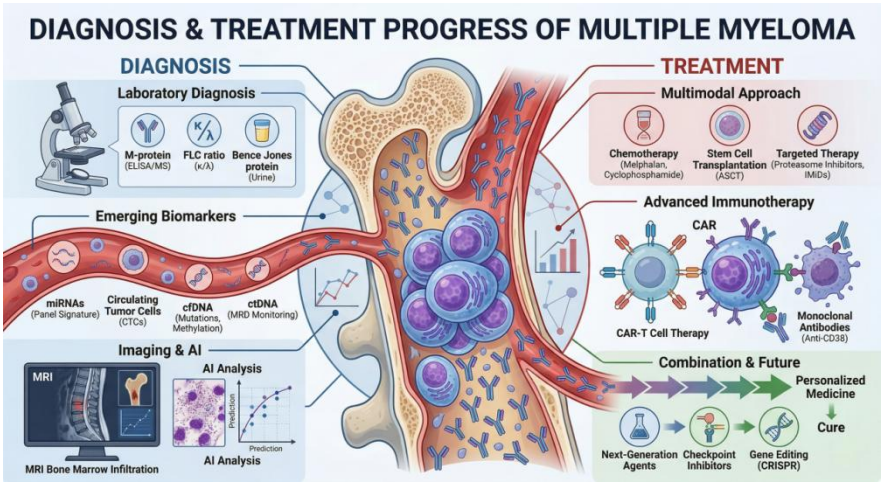

Figure 1 An Overview of Multimodal Diagnosis and Treatment Progress in Multiple Myeloma

2 DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Multiple myeloma is a malignancy characterized by the abnormal proliferation of plasma cells and subsequent bone marrow infiltration. Accurate diagnostic criteria are paramount for the timely initiation of treatment and patient management. Currently, the widely adopted international diagnostic criteria for MM are primarily based on clinical manifestations, laboratory examinations, and bone marrow biopsy results.

Clinical Presentation: Patients frequently exhibit symptoms such as bone pain, fatigue, anemia, and pathological fractures. Additionally, renal impairment, recurrent infections, and neurological deficits may also occur.

Laboratory Investigations: Common hematological abnormalities include anemia, hyperviscosity, and hypercalcemia. Serum and urine protein electrophoresis, along with immunofixation electrophoresis, can detect the presence of monoclonal immunoglobulins. In urinalysis, the abnormal secretion of light chain proteins (Bence Jones proteins) serves as a diagnostic indicator.

Bone Marrow Biopsy: This is the definitive step in confirming MM. By evaluating the quantity and morphology of plasma cells, as well as the heterogeneity and clonality within the bone marrow, the presence of MM can be conclusively established.

Based on these parameters, the most commonly utilized international guidelines are those established by the International Myeloma Working Group (IMWG) [3]. According to the IMWG criteria, a diagnosis of MM requires the presence of any two of the following criteria: a bone marrow clonal plasma cell percentage of ≥10%, the presence of serum or urinary monoclonal immunoglobulins (or Bence Jones protein), evidence of osteolytic bone lesions, and an abnormal serum free light chain (κ/λ) ratio.

3 LABORATORY DIAGNOSIS OF MULTIPLE MYELOMA

Biomarkers refer to specific molecules or substances that emerge during the onset and progression of a disease, which can be utilized for diagnosis, prognostic evaluation, and the selection of therapeutic regimens.

3.1 Monoclonal Immunoglobulin (M-protein)

A hallmark of MM is the presence of excessive M-proteins or their polypeptide chain subunits in the blood or urine. The M-protein is one of the most critical biomarkers in MM, holding significant importance in its diagnosis, treatment, and prognosis. According to research by Zhang et al., the expression level of M-protein in MM patients is closely correlated with disease staging, therapeutic efficacy, and prognosis [4]. Therefore, quantifying the serum M-protein level is of vital significance.

Furthermore, studies by Wu et al. suggest that M-proteins play a crucial role in the pathogenesis of MM. In the early stages of the disease, M-protein expression is relatively low, but it progressively elevates as the disease advances. This may be associated with the M-protein's involvement in the proliferation and apoptosis of MM cells, as well as the impairment of vascular endothelial cells [5]. Consequently, monitoring M-protein levels is essential for understanding disease progression and formulating therapeutic strategies.

Currently, common clinical methods for detecting serum M-protein include enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, and mass spectrometry. These methodologies possess respective advantages and limitations, and issues of false negatives and false positives remain. These discrepancies may be attributed to pre-analytical factors such as sample collection and handling, as well as laboratory quality control. Therefore, further optimization of detection methodologies is required to enhance diagnostic accuracy, and the development of novel, highly sensitive assays represents a current hotspot in research.

3.2 Emerging Biomarkers

3.2.1 MicroRNAs (miRNAs)

The utilization of miRNAs as a diagnostic tool for MM possesses significant necessity and potential advantages [6]. Given that MM is a highly heterogeneous disease, traditional diagnostic modalities may fail to comprehensively assess disease characteristics. As critical molecules regulating gene expression, miRNAs exhibit substantial potential in reflecting the heterogeneity and progression of MM [7]. Furthermore, miRNAs can be obtained through non-invasive or minimally invasive sampling methods (e.g., blood, urine). Compared to traditional tissue biopsies, miRNA detection significantly reduces patient discomfort. Concurrently, miRNAs can be detected at low concentrations, offering high sensitivity, and display specific expression profiles across different tumor types. Because miRNAs possess the capacity to regulate multiple targets simultaneously, detecting a panel of miRNAs to form a specific signature can enhance diagnostic reliability. Beyond diagnosis, analyzing miRNA target genes can provide profound insights into the molecular mechanisms underlying MM, forming a theoretical foundation for novel therapies [8].

However, the clinical application of miRNAs still faces challenges, including the standardization of sample collection, analytical methodologies, and the need for large-scale clinical validation. Future research should prioritize addressing these hurdles.

3.2.2 Circulating tumor cells (CTCs)

Circulating tumor cells are cells shed from the primary tumor into the peripheral bloodstream. In MM, CTC detection has emerged as a promising biomarker application [9]. By capturing and isolating CTCs from the blood, malignant cells can be detected even when bone marrow tumor burden is low. The enumeration and characterization of CTCs can be employed to monitor disease progression; as the disease advances, the CTC burden typically increases. Concurrently, the phenotypic and genotypic characteristics of CTCs can provide insights into molecular features, aiding in the assessment of disease activity and prognosis [10]. Elevated CTC levels are often correlated with adverse outcomes. Moreover, tracking longitudinal changes in CTCs during treatment can help evaluate therapeutic efficacy, identify emerging drug resistance, and facilitate personalized therapy [11]. Challenges persist regarding the standardization of CTC capture platforms and addressing biological heterogeneity, but CTCs are poised to become a vital tool in clinical management.

3.2.3 Cell-Free DNA (cfDNA)

The analysis of cell-free DNA can be utilized to detect genetic mutations in MM. Analyzing cfDNA in peripheral blood provides information regarding specific genetic mutations within tumor cells [12]. This facilitates molecular subtyping, predicting disease progression, and guiding targeted therapy. Secondly, cfDNA analysis enables the detection of genomic rearrangements—structural variations prevalent in MM clonal plasma cells [13]. Concurrently, the methylation profiling of cfDNA holds diagnostic potential, as specific DNA methylation signatures may correlate with disease prognosis [14]. Furthermore, routine longitudinal monitoring of blood cfDNA allows clinicians to assess disease activity and adjust treatment regimens. Technologies for cfDNA are still evolving, and standardization and clinical validation remain ongoing challenges.

3.2.4 Circulating tumor DNA (ctDNA)

Circulating tumor DNA (a specific subset of cfDNA) demonstrates promising utility in monitoring disease progression and treatment response [15]. Routine analysis of ctDNA facilitates the assessment of disease activity. Crucially, ctDNA analysis can guide targeted therapy by identifying specific actionable genetic mutations or chromosomal rearrangements [16]. Furthermore, ctDNA detection is highly valuable for monitoring Minimal Residual Disease (MRD) [17]. Assaying blood ctDNA can determine the presence of MRD at an earlier stage than conventional modalities, allowing for serial monitoring post-treatment to provide a more precise evaluation of efficacy and patient prognosis. Despite challenges in optimizing analytical sensitivity and specificity, ctDNA possesses vast prospective applications.

3.3 Imaging Diagnostic Techniques: MRI

Compared to other imaging modalities, Magnetic Resonance Imaging (MRI) exhibits superior sensitivity for the early detection of myeloma cell infiltration, as its mechanism is based on the analysis of tissue water and fat content [18]. Consequently, MRI facilitates early diagnosis. While MM patients frequently experience skeletal involvement, MRI can identify affected bone marrow prior to the onset of overt trabecular bone loss. For detecting diffuse bone marrow involvement, MRI is demonstrably more effective than PET/CT. MRI of the spine and pelvis is highly beneficial, detecting focal lesions in approximately 90% of MM cases [19]. Furthermore, MRI is indispensable for differentiating malignant pathological fractures from benign fractures. However, limitations exist, including prolonged acquisition times, high costs, contraindications for patients with metallic implants, challenges with claustrophobia, and a restricted field of view.

3.4 Application of Artificial Intelligence (AI) in MM Diagnosis

Artificial Intelligence (AI) can be robustly applied to the analysis of bone marrow smears and radiological images in MM. By training machine learning models on vast datasets, the automated detection of abnormal cells and relevant morphological features can be achieved [20]. This significantly enhances the speed and accuracy of interpretations. Moreover, machine learning models can integrate multimodal data—clinical parameters, molecular profiles, and imaging—to predict prognosis and disease progression risks, assisting clinicians in formulating personalized regimens [21]. Data mining techniques enable the extraction of latent patterns from large-scale MM datasets, instrumental in

discovering novel biomarkers and therapeutic targets [22,23]. By continuously monitoring patients, AI models can forecast therapeutic responses and drug resistance, optimizing overall treatment efficacy [24]. Ultimately, AI synthesizes individual genomic and clinical data to deliver highly personalized recommendations, maximizing outcomes while minimizing risks.

4 TREATMENT OF MULTIPLE MYELOMA

The management of MM necessitates a comprehensive, multimodal approach tailored to the patient's specific disease characteristics, age, and health status.

Chemotherapy: A foundational treatment. Commonly utilized agents include Melphalan, Cyclophosphamide, Vincristine, and Doxorubicin. Chemotherapy exerts cytotoxic actions on myeloma cells to alleviate symptoms and control disease progression [25].

Stem Cell Transplantation: The most frequently employed approach is Autologous Stem Cell Transplantation (ASCT). This involves harvesting the patient's hematopoietic stem cells, administering high-dose conditioning chemotherapy to eradicate myeloma cells, and reinfusing the stem cells to rescue bone marrow function.

Targeted Therapy: Utilizes pharmacological agents designed to interact with specific molecular targets. These encompass proteasome inhibitors (e.g., Bortezomib, Carfilzomib), immunomodulatory drugs (e.g., Thalidomide, Lenalidomide), and anti-CD38 antibodies. These agents disrupt the growth and survival mechanisms of myeloma cells [26].

Immunotherapy: A transformative approach leveraging the patient's immune system. Common modalities include monoclonal antibody therapy (e.g., Daratumumab, Elotuzumab), which target specific surface antigens to induce apoptosis and recruit immune effector cells [27].

CAR-T Cell Therapy: A revolutionary advancement utilizing genetically engineered T cells to specifically recognize and eliminate myeloma cells [27]. CAR-T therapy has demonstrated remarkable efficacy, particularly in relapsed or refractory MM.

Beyond these modalities, management may incorporate radiotherapy (for localized disease control and bone pain), surgical interventions (to stabilize fractures), and supportive care (analgesics, bone-modifying agents, antimicrobials). MM treatment is a dynamic, protracted process, and regimens must be continuously personalized based on evolving clinical status.

5 CONCLUSION AND FUTURE PERSPECTIVES

Looking forward, with the continuous emergence of novel therapeutic modalities—such as advanced molecular targeted therapies, next-generation chemotherapeutics, and immune checkpoint inhibitors—the diagnosis and treatment of MM are poised to achieve remarkable breakthroughs. Innovative interventions like CAR-T cell therapy and specific cytokine inhibitors enable highly personalized treatment strategies tailored to patients at varying disease stages, substantially improving survival rates. Concurrently, as gene-editing technologies mature, genetically modified effector cells may acquire the capacity to mount more precise attacks against myeloma cells, expanding the clinical armamentarium.

In conclusion, the diagnosis and management of multiple myeloma remain a protracted and complex endeavor. Sustained, in-depth research and the relentless exploration of novel therapeutic avenues are imperative to ultimately enhance the survival rates and advance towards a potential cure for patients afflicted with multiple myeloma.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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