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A STUDY TO IDENTIFY NOVEL BIOMARKERS ASSOCIATED WITH MULTIPLE MYELOMA

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Abstract

Background. Multiple Myeloma (MM) is a plasma cell cancer that affects white blood cells. Plasma cells from the bone marrow grow abnormally, as a consequence of which patients have high amounts of monoclonal immunoglobulin in their blood and urine, poor renal function, and recurring infections due to this condition. Osteolytic bone lesions and immunodeficiency also impact multiple myeloma patients' longevity and quality of life. The disease accounts for 13 % of all hematological malignancies worldwide, making it the second most common blood cancer. **Material and Methods.** The studies investigating MM biomarkers from 2000 to 2021 are collected from various databases. "Multiple myeloma", "biomarkers", "genetic markers", "prognostic markers", "Epidemiology of multiple myeloma", and "risk factors for multiple myeloma" are the key phrases utilized to gather the articles. **Results.** The scientific and medical research progressed into MM, and the number of cases increased over time and continues to rise, prompting researchers and clinicians to discover new consequences of the disease and new markers for prognosis, diagnosis, detection, and treatment of cancer in the earliest stages. Prognostic and predictive signs for illness recurrence and response to medication may be detected adequately by innovative potential biomarkers, which are more accurate than current approaches. **Conclusion.** Treatment for multiple myeloma includes a variety of chemotherapeutic medicines, including immune modulators and proteasome inhibitors; however, most patients still experience recurrence after completing treatment. There have been numerous novel techniques for managing multiple myeloma, and this review summarises the most commonly used and the new ones that have appeared in the previously published articles.

Key words: multiple myeloma, biomarkers, therapeutic targets, prognosis.

ИССЛЕДОВАНИЕ НОВЫХ БИОМАРКЕРОВ, СВЯЗАННЫХ С МНОЖЕСТВЕННОЙ МИЕЛОМОЙ

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Аннотация

Актуальность. Множественная миелома (ММ) – злокачественная опухоль плазматических клеток, поражающая лейкоциты. У пациентов с ММ аномалии в плазматических клетках костного мозга приводят к повышению уровня моноклонального иммуноглобулина в крови и моче, с развитием почечной недостаточности и появлению рецидивирующих инфекций. Остеолитические поражения и иммунодефицит также оказывают негативное влияние на продолжительность и качество жизни пациентов с множественной миеломой. На это заболевание приходится 13 % всех злокачественных гематологических опухолей в мире, что делает ММ вторым наиболее распространенным новообразованием кроветворной системы. **Материал и методы.** В различных базах данных проведен поиск опубликованных результатов исследований, посвященных биомаркерам ММ, за период с 2000 по 2021 г. При отборе статей исполь-

зовались следующие ключевые понятия: «множественная миелома», «биомаркеры», «генетические маркеры», «прогностические маркеры», «эпидемиология множественной миеломы», «факторы риска множественной миеломы». **Результаты.** Несмотря на значительные успехи, полученные в изучении и лечении ММ, число больных с этой патологией продолжает расти, побуждая исследователей к поиску новых маркеров для прогноза, диагностики и лечения заболевания, особенно на ранних стадиях. Прогностические и предиктивные факторы риска рецидива заболевания и ответа на терапию могут быть выявлены с помощью более эффективных инновационных методов определения потенциальных биомаркеров. **Заключение.** Несмотря на применение различных противоопухолевых препаратов, включая иммуномодуляторы и ингибиторы протеасом при лечении множественной миеломы, у большинства пациентов наблюдаются рецидивы заболевания. В обзоре проанализированы современные методы лечения множественной миеломы, как наиболее часто используемые, так и новые, представленные в недавно опубликованных статьях.

Ключевые слова: множественная миелома, биомаркеры, терапевтические мишени, прогноз.

Introduction

Plasma cell myeloma, another name for multiple Myeloma, is a malignancy that targets clonal plasma cells (PC). MM patients had plasma cells in their peripheral circulation [1]. A malignant cell is formed in the bone marrow (BM) when lymphocytes develop in lymph nodes. There is a considerable invasion of the skeletal system, including hypercalcemia, anemia, and osteolytic lesions caused by PC's abnormal proliferation BM malignancy is denoted by the term "myeloma", whereas the prefix "multiple" alludes to multiple organ involvement [2]. Approximately 13 % of all hematological malignancies are attributed to MM, the second most prevalent blood cancer. About 230,000 cases of MM were reported in the U.S. between 2011 and 2016 [3]. The survival rate for this condition is 30 months, which might increase significantly with Thalidomide therapy, BM transplantation, [4] osteolytic bone lesions, and immunodeficiency harm MM patient's life. Of patients with this condition has almost doubled to about 50 %, but the illness is still considered incurable. Age, gender, obesity, ionizing radiation exposure, and a family history of MGUS are all established risk factors. It has been reported that there may be a biological component to MM. Multiple myeloma is diagnosed using biomarkers used for decades [5].

Global Scenario and Risk Factors of Multiple Myeloma

According to the Global Cancer Observatory, over 160,000 persons were diagnosed with MM in 2018 – around 2.1 and 1.44 cases per 100,000 males and women, respectively, with age-adjusted incidences. Australians, Western Europe, and Americans are most likely to be affected by the disease. Around 32,000 new cases are discovered in the United States in 2020, accounting for 1.8 % of this region's total cancer diagnoses [6]. The current incidence rate of 7.0 per 100,000 people represents an increase of more than 143 % compared to the 1975 rate of 4.9 per 100,000 people [7]. When the population's age is considered, the global incidence and mortality rates are 2.1 and 1.39 per 100,000 people, respectively. The lowest rates

of occurrence were recorded in China (0.92 %), South Korea (0.54 %), Saudi Arabia (1 %), and India (1 %). New Zealand had a rate of 5.3 %, Australia had a rate of 5.0 %, the United Kingdom had a rate of 4.3 %, Israel had a rate of 4.2 %, and Norway had a rate of 4.2 % [8].

Multiple myeloma is a cancer that affects older people, with the typical age of diagnosis in the United States being 69. Over 60 % of diagnoses are made in people over 65, while less than 15 % are in those under 55 [9]. The typical age of death is 75, with that over 65 accounting for about 80 % of all deaths. It is expected that the accumulation of mutations leading to MM would take decades, making the disorder clinically evident only in the elderly [7]. Although MM family history clusters have been identified, the fundamental gene modifications remain unknown [10]. Globally, men are more likely to be affected than women. However, none of these risk variables has been established in MM. The increased incidence of obesity among males is ascribed in part to risky habits such as reading liquor labels, smoking, and excessive alcohol use [11]. The incidence of HIV in African Americans was 16.5 per 100,000 men and 12.0 for every 100,000 women [12], which was higher than in whites. Asian men were found to have a risk factor of 5.0, while Asian women were found to have a risk factor of 3.2. The mortality rate from MM was higher among African American men and women than among Caucasians, with 7.5 and 5.3 fatalities per 100,000 people, respectively [13].

Molecular Pathogenesis and Current Biomarkers of MM

Several genetic changes are linked to the development of MM, while the specific cause is unclear. PCs' intraclonal genetic heterogeneity aids the disease's progression. While specific oncogenes and mutations were linked to the development of MGUS, others were related to the progression of MGUS to MM or extramedullary MM. Moreover, it was revealed that chromosomal differences substantially impacted treatment effectiveness, drug resistance, and MM prognosis [14]. An estimated rate of 1–2 % with MGUS progress to MM every year, and this

transition is likely due to the presence of mutational diversity in MM cell populations. There is a theory that multiple myeloma cells begin life as single tumors and then divide into several lesions, resulting in multiple myelomas [15]. Between MGUS and MM, smoldering multiple Myeloma (SMM) is a clinical-stage when multiple myeloma develops. High serum or urine monoclonal protein levels and 10 % to 60 % clonal PCs from BM are myeloma hallmarks without additional myeloma-defining characteristics such as hypercalcemia, renal insufficiency, or anemia [16]. Because of clonal evolution and treatment resistance, plasma cell leukemia (PCL) may become an aggressive, bone-marrow-independent condition. Clonal expansion and treatment resistance may cause MM to progress to plasma cell leukemia, a more aggressive and bone marrow-independent form of the disease. Plasmacytomas are formed outside of the bone marrow in PCL patients because of the proliferation and spread of MM cells in the bloodstream. In the bone marrow microenvironment (BMM), the accumulation and osteolysis of MM may be inhibited by therapies now in use, and new ones are being studied to enhance patient health and lifespan [17]. The BMM is thought to affect cancer and multiple myeloma. BMM-derived MM cells may infiltrate, establish, multiply, adhere, and migrate when dormant [18]. Anti-inflammatory mediators, such as the adipokine and growth factors produced by the body's fat, may also affect inflammation. A wide range of factors enhances the formation of malignant cells and the resistance of healthy cells to drugs and cytotoxicity [19].

Multiple myeloma biomarkers approach

Plasma cells in the bone marrow play a vital role in developing this disease and are classified as a form of blood cancer. As a complex disease, biomarkers can provide insight into its progression and development of effective treatments. Multiple myeloma biomarkers can be identified through the following approach:

i) Genomic analysis

The genomic profile has also been linked to the patient's prognosis in several extensive cohort studies of patients with MM [20, 21]. In addition, specific genomic abnormalities have been attributed to the molecular pathogenesis of MM, which might influence the efficacy of therapeutic interventions [22]. As genomic studies develop, this could probably include improving the prognosis and identifying predictive factors of response and actionable mutations that may aid in selecting treatment options.

ii) Integration of genomic and clinical data

Biomarkers are present in human fluids and tissues, in addition to imaging, which may be utilized as a diagnostic, prognostic, and predictive tool. They are divided into genomes, transcriptomics, proteomics, and clinicopathologic. Prognostic and diagnostic biomarkers do exactly what their names indicate, while predictive biomarkers anticipate clinical outcomes

by assisting with therapy selection and optimization, ensuring that certain therapies are likely to be beneficial. A prognosis for patients suffering from multiple myeloma remains uncertain despite an increasing number of biomarkers becoming available as well as improved has not been enough information available to use biomarkers routinely to guide treatment for multiple myeloma, treatment for high-risk MM may be intensified or reduced, depending on the patient's risk to switch to another treatment approach entirely [23]. A genomic analysis is completed, then the genomic data is integrated with the patient's clinical data. Thus, this will enable researchers to identify genetic mutations associated with particular clinical characteristics.

iii) Machine learning algorithms

Over the past few years, machine learning algorithms and deep learning procedures have been increasingly applied to detecting tumors [24–27], as they can combine proteomic, genomic, histopathology, and image data to improve cancer patients' diagnosis and treatment options. However, the objective of Deep Learning (DL) or Machine Learning (ML) is not to replace human capability but to provide a decision-support system for oncologists in their practice. The effectiveness of these procedures has been demonstrated in both the treatment of solid tumors and hematological disorders. In recent years, numerous reports have shown their role in diagnosing, prognosis, and therapeutic evaluating hematological neoplasms. There are an increasing number of cases of MM per year due to its growing prevalence as a hematological tumor that occurs when plasma cells multiply clonally. A further disadvantage of MM is that while survival has improved upon diagnosis, its outcome is essentially negative [28, 29]. As a result, machine learning algorithms can be used to identify patterns and correlations between genetic alterations and clinical data. Multiple myeloma is a disease that can be diagnosed, prognosis, and treated with the identification of potential biomarkers.

iv) Functional validation

Due to the extensive list of potential biomarkers, biomarker validation studies are susceptible to false positives. It is essential to remain sensitive to methodologies that may increase the possibility of false negatives. However, limiting the number of false positives is also necessary to prevent a proliferation of unreproducible biomarker results in the literature. The multi-simultaneous comparison should be conducted to minimize false discovery and maximize the power to detect significant associations. A critical part of developing a multiple-comparison methodology was controlling the family-wise error rate [30]. A large patient cohort may be used to validate potential biomarkers to ensure their accuracy and reliability, and it will be possible to examine the functional relevance of potential biomarkers once they have been validated. The biomarkers may be evaluated in vitro or in vivo using various models to determine how they influ-

ence multiple myeloma cells' growth, proliferation, and survival.

v) Clinical trials

There are around 35 nonsynonymous mutations in the DNA of each patient with multiple myeloma. The extensive panorama of genomic alterations is further defined by several disrupted important signaling networks and mutations with diagnostic and therapeutic significance. Several potential avenues exist for optimizing clinical trials for biomarkers in MM based on risk-adapted strategies [31, 32]. Disease-related biomarkers assist in diagnostic, prognostic, and response monitoring purposes.

Meanwhile, drug-related biomarkers provide information about an individual's ability to benefit from a particular drug and how the body will respond. Clinical trials define integral biomarkers as markers that must be measured in real-time to proceed with the practice, and used to identify early responses to determine the next steps [33]. Finally, clinical trials can be conducted on these biomarkers to evaluate their efficacy in developing new treatments for multiple myeloma based on their effectiveness as potential targets for development. This approach aims to identify potential biomarkers for multiple myeloma by combining genomic analysis, clinical data integration, machine learning algorithms, and validation. The findings of this study could be helpful for better understanding the disease, improving diagnosis and prognosis, and developing new treatments that target specific molecular pathways involved in the condition.

The significant biomarkers of Multiple myeloma

i) Novel Prognostic Biomarkers in Multiple Myeloma

While presently utilized biomarkers for diagnosis and prognosis continue to increase the number of MM cases, various next-generation biomarkers are now being developed to potentially improve clinical care and the outcome of the illness. Biomarkers and their underlying molecular processes will be discussed in the following sections. These markers are shown to be helpful in forthcoming approaches to diagnosing early. Despite the present diagnostic and prognostic biomarkers being employed due to the steadily growing number of MM patients, several next-generation biomarkers that may improve clinical care and the course of the illness are now emerging. The following sections provide the most current biomarkers and underlying biological processes. Also, we highlight their strengths and potential for inclusion in future recommendations for accurate illness evaluation and early detection [34].

ii) Genomic Markers

Modifications in the cytogenetics were included in the updated international staging system (ISS), showing their importance in the evaluation of MM. There have been more reports of mutation and translocation in chromosomes that may be used as markers in mul-

multiple myeloma. Patients with various Myeloma (MM) who had chemotherapy-induced peripheral neuropathy [35] were discovered to have genetic changes that were connected with their outcomes and survival [36]. CNVs, including hyper diploidy, chromosomal arm loss or gain, along with chromosome 14 translocations that disrupt the immunoglobulin heavy chain region, are hallmarks of the etiology of MM [37]. Because the immunoglobulin heavy chain enhancer now controls the partner genes, the fusion product of immunoglobulin results in the overexpression of oncogenes [38]. Secondary events that occur as the illness progresses include MYC oncogene translocations. In MM, the Ig locus is only involved in 30 % of MYC translocations, which is unusual compared to the other translocations [39]. Cytogenetics has been a critical predictive biomarker in the risk categorization of patients; the combination of two markers that indicate unfavorable outcomes might make the disease course unexpected [40]. There is a need for innovative biomarkers for targeted treatment since they can help with regimen selection.

To summarize, the utilization of genomic biomarkers in multiple myeloma holds immense promise for advancing the diagnosis, prognosis, and treatment of this complex hematological malignancy. These biomarkers provide crucial insights into the underlying genetic alterations and molecular mechanisms driving the disease, allowing for more precise patient stratification and personalized therapeutic strategies. By identifying high-risk patients earlier and tailoring treatment plans based on individual genomic profiles, healthcare professionals can enhance the effectiveness of interventions while minimizing unnecessary side effects. Moreover, genomic biomarkers enable researchers and clinicians to better understand disease progression, drug resistance, and relapse patterns. This increased knowledge aids in the development of new targeted medicines as well as the optimization of current therapy regimens, eventually improving patient outcomes and quality of life. Furthermore, the integration of genomic data into clinical practice facilitates the ongoing evolution of precision medicine, fostering a shift towards more proactive and informed medical decisions. As technology advances, the discovery and validation of new genetic biomarkers may lead to the identification of novel therapeutic targets and the design of novel clinical trials. While challenges remain, such as the need for standardized testing protocols and robust data interpretation frameworks, the benefits of leveraging genomic biomarkers in multiple myeloma are undeniable. The field stands poised for remarkable progress as these biomarkers contribute to a new era of personalized and effective care for patients with multiple myeloma [41].

iii) Gene expression Profiling

Several studies have employed gene expression profiling (GEP) to assess the molecular heterogeneity of MM, measure the expression level of a collection of

genes, and connect those expression levels to clinical outcomes [42]. Newly diagnosed patients' CD138+ plasma cells showed upregulation of 51 genes and downregulation of there were 19 genes, 30 % of which were on chromosome 1 (1p and 1q). C-reactive protein, microglobulin two, lactate dehydrogenase, and microglobulin two levels were positively correlated with the 70-gene model score and could reliably predict disease-free survival. Using 17 genes, an equivalent prognostic model could be developed. To better understand how the proliferation rate of MM develops from monoclonal gammopathy of undetermined significance (MGUS), the third study used the gene expression-based proliferation index model to overt early- and late-stage Myeloma. Using this paradigm, researchers discovered proliferation genes that differed in expression between malignant myeloma cell lines that proliferated and non-malignant plasmablastic cells, as well as between non-proliferating normal plasma and memory B cells [43]. In myeloma patients receiving high-dose chemotherapy and autologous stem cell transplantation, this index of proliferative genes proved to be an effective predictive tool for event-free and overall survival. The index was also independent of MM's most important clinical risk factors. Other GEP studies of various myeloma populations found that GEP might be a useful method for MM risk assessment [44, 45].

GEP enhances the precision of disease monitoring, allowing for early detection of relapse and minimal residual disease. Its ability to capture dynamic changes in gene expression patterns over time equips healthcare professionals with valuable insights for making informed clinical decisions, optimizing treatment regimens, and maximizing long-term remission rates. The integration of GEP data with other omics technologies and clinical parameters further enriches our understanding of MM's heterogeneity, paving the way for more robust risk stratification models and refined patient management strategies. As our knowledge of MM continues to evolve, gene expression profiling stands as a pivotal tool in unraveling its complexities and advancing the frontier of personalized medicine in the treatment of multiple myeloma [46].

iv) Proteomic markers

Prognostic and diagnostic potentials of protein expression have been shown in patients with MM. Various studies have shown that the serum of individuals with multiple myeloma has varying levels of several proteins, including apolipoprotein A-1, transferrin, plasma kallikrein, haptoglobin, and serum amyloid A protein, integrin alpha-11, sulfhydryl oxidase 1, [47]. In patients with delayed response to bortezomib-based treatment, proteins implicated in inflammation and apoptosis were down-regulated, whereas proteins involved in the proteasome activation were up-regulated [48]. Thalidomide response in patients with MM may be predicted using proteins such as vitamin D-binding protein and amyloid A protein. They all showed func-

tional diagnostic and prognostic potentials when used together. However, before they can be used in clinical settings, they must be thoroughly validated [49].

Proteomic markers offer a more comprehensive and detailed view of the disease at the molecular level, enabling earlier and more accurate detection, classification, and monitoring of multiple myeloma. These markers can facilitate personalized medicine approaches by aiding in the identification of specific disease subtypes and guiding the selection of tailored therapies. Additionally, proteomic profiling can help elucidate the underlying mechanisms of disease progression, drug resistance, and relapse, leading to the development of novel therapeutic targets and strategies. Furthermore, the non-invasive nature of proteomic analysis, often relying on easily accessible bodily fluids such as blood or urine, enhances patient convenience and reduces the need for invasive procedures. This not only improves patient comfort but also allows for more frequent and timely monitoring, thereby optimizing treatment adjustments and improving overall patient outcomes. While challenges such as standardization, data interpretation, and cost-effectiveness remain, ongoing advancements in proteomic technologies and bioinformatics are addressing these issues and fostering the integration of proteomic markers into clinical practice. Ultimately, the integration of proteomic markers into the management of multiple myeloma holds the potential to revolutionize the field by enabling more precise, personalized, and effective approaches to diagnosis and treatment, ultimately improving the quality of life and prognosis for individuals affected by this challenging disease [50].

v) Angiogenic markers

Angiogenesis, also known as neovascularization, is the formation of new blood capillaries from pre-existing vascular tissue. Because cancer needs enough blood flow to develop and progress, it is directly connected to tumors [51]. Growth factors, oxygen sensors, endothelial sensors, angiopoietins, and junctional molecules play a role in angiogenesis signaling, resulting in the dynamic and diverse process of angiogenesis [52]. VEGF is the most well-known, researched, and effective angiogenic activator; most chemotherapy drugs are directed toward it. The expression of VEGF has been elevated in various malignant tissues and surrounding stroma, indicating that it plays a vital role in neovascularization [53]. Pro-angiogenic factors, including VEGF, Angiopoietin-1, Angiopoietin-2, and HGF, are overexpressed in MM that might be used as diagnostic indicators [54]. Myeloma therapeutics have also investigated angiogenic factors as a therapeutic target in addition to conventional chemotherapy regimens. After treatment with cinnamon extract, there was a considerable reduction in the molecular expression of pro-angiogenic factors, including VEGF, Ang-1, and Ang-2. These results highlight the importance of biomarkers for various malignancies, including MM [55].

The benefits of utilizing angiogenic markers in multiple myeloma are multifaceted. Firstly, these markers

offer valuable insights into disease prognosis and risk stratification. Higher levels of angiogenic markers have been correlated with aggressive disease behavior, shorter progression-free survival, and overall poor prognosis in multiple myeloma patients. Secondly, angiogenic markers hold the potential as predictive indicators for therapeutic response. Studies have demonstrated that elevated angiogenic marker levels may predict resistance to conventional treatments and targeted therapies. This allows for tailored treatment strategies, optimizing patient outcomes. Furthermore, angiogenic markers serve as potential targets for novel therapeutic interventions. Inhibition of angiogenesis has been explored as a treatment approach for multiple myeloma, with promising preclinical and early clinical results. Targeting angiogenic pathways could not only impede tumor growth but also sensitize the tumor microenvironment to existing therapies, potentially overcoming treatment resistance [2, 56].

vi) Immune markers

Every physiological and pathological state relies on immune cells. In the tumor niche, an immunosuppressive environment is created by the imbalance of the immune system, allowing tumor cells to proliferate uncontrolled due to the differences in immune cells. Lenalidomide and pomalidomide, two immunomodulatory imide drugs (IMiDs), are the first step in modern immunotherapy based on this imbalance in immunological characteristics in MM. Anti-CD38 and anti-SLAMF7 monoclonal antibodies were subsequently approved for treatment in recurrent MM patients. In MM, the bone marrow's immunosuppressive microenvironment is characterized by the downregulation of T-cell effectors, an increase in T-regulatory cells (Treg), and myeloid-derived suppressor cell expression. T and B cells cannot be activated by inhibitory cells; they contribute to the tumor escape mechanism in multiple myeloma [57]. Numerous immunological markers in MM were shown to be deregulated in cancer.

PD-1 expression on plasma cells has grown considerably in patients with multiple myeloma, with the highest levels reported in relapsed MM patients [2]. In MM, the expression of PD-1 in NK and T-cells was similarly more significant – Myeloma cell growth suppression in both PD-1/PD-L1 defective animals and mice treated with anti-PD-L1 antibodies [58]. Sustained expression of PD-L1 in the bloodstreams of individuals with MM may serve as a prognostic indicator [59]. Similarly, PD-1 and CTLA-4 overexpression is associated with increased immunosuppressive cells like Tregs in the BM of patients with MM. They provide information on myeloma's development that might be useful for identifying the disease early on, determining a patient's prognosis, or developing new treatments [60].

The integration of immune markers into the diagnosis, prognosis, and treatment strategies for multiple myeloma has emerged as a promising avenue to enhance patient management and outcomes. Immune markers, encompassing various components of the

immune system such as T cells, natural killer cells, cytokines, and immune checkpoint molecules, offer valuable insights into the tumor microenvironment, disease progression, and response to therapy. The benefits of utilizing immune markers in multiple myeloma are multifaceted. Firstly, immune markers can aid in risk stratification and prognosis, enabling clinicians to identify patients with aggressive diseases who may require more intensive therapeutic interventions. Secondly, immune markers can inform treatment decisions, helping to tailor therapies based on the immune profile of the patient and the tumor microenvironment. This personalized approach has the potential to enhance treatment efficacy while minimizing unnecessary side effects. Furthermore, immune markers can serve as surrogate endpoints in clinical trials, facilitating the evaluation of novel immunotherapies and targeted interventions. As the field of immunotherapy continues to evolve, incorporating immune markers as biomarkers of treatment response can expedite drug development and approval processes [61–64].

vii) miRNA biomarkers for multiple myeloma

The small non-coding RNA fragments known as microRNAs (miRNAs) control the expression of genes post-transcriptionally. RNA polymerase II (Pol II) is primarily responsible for their transcription, producing pri-miRNAs, the predecessors of “hairpin” structures. A stem-loop form with a length of around 70 base pairs (pre-miRNAs) is created when Drosha, a particular double-stranded RNA endoribonuclease, cuts the pri-miRNAs. Using exportin 5, pre-miRNAs are actively carried to the cytoplasm, cleaved by Dicer1, another RNase III type endonuclease, to produce a 20-nucleotide miRNA duplex. Due to the absence of a loop between the 30 and 50 arms, duplex miRNAs – molecules with two strands are made (miRNAs-3p and miRNAs-5p). The RNA-induced silencing complex (RISC), essential for suppressing specific genes' expression during RNA interference, is formed when mature miRNAs are specifically coupled with the Argonaute AGO2 protein.

MiRNAs inhibit translation or destabilize the target mRNA by attaching to the 30-UTR region of the mRNA. The mRNA is cut when complete complementarity with the 30-UTR region exists. Other miRNAs can prevent the translation by connecting to the 5' UTR region or the RNA region, forming the open reading frame [65]. On chromosomes, fragile areas are frequently where miRNA genes are found. Tumor cells often exhibit a shift in the expression of the miRNA gene, which translocations, amplifications, or deletions may bring on. Target genes' expression is altered as a result of these modifications. MiRNAs can act as carcinogenic oncomirs or suppressors blocking oncogenes depending on the genes they regulate. MiRNAs may be valuable biomarkers for detecting, assessing, and treating cancer. MiRNAs appear to be a promising study field for novel treatment targets in MM, given the intimate relationship between miRNA expression abnormalities and MM progression [66, 67].

viii) Advanced Methodologies in Next-Generation Biomarkers

While the development of next-generation biomarkers is still in its early stages, they have the potential to fundamentally alter the diagnosis and treatment of MM. As a result, these new approaches may be able to provide earlier diagnosis, a more accurate prognosis, and a more personalized treatment plan. Research in this area is expected to advance in the future, which will enable cutting-edge techniques to play a more prominent role in controlling multiple sclerosis.

a) Flow Cytometry

In recent years, flow cytometry (FC) has quickly shifted from fundamental research to clinical applications due to its unique properties regarding cell analysis. Current applications of flow cytometry in cancer research include identifying tumor cells, identifying aneuploidy in DNA, analyzing cell proliferation, and phenotyping cancer cells [68]. By assessing minimal residual disease (MRD) following MM treatment, specific markers are utilized to determine remission status.

b) Next-Generation Sequencing (NGS)

NGS testing for cancer is becoming increasingly prevalent owing to the ability to rapidly sequence a large number of genes and the effectiveness in linking genomic anomalies with therapeutic indications. However, there are several limitations to how NGS testing influences cancer. While NGS has been correctly focused on gene alterations, it has not evaluated the impact of clinical factors such as patients' general health on test-related outcomes. Similarly, the cost-effectiveness of NGS in contrast to single-gene testing has been evaluated [69]. Over the last decade, next-generation sequencing has become a widely used technique in clinical oncology due to the advancement of advanced sequencing technology. Cancer mutations can be identified using NGS, and the molecular rationale for targeted therapies can be characterized using NGS. NGS costs are much lower than conventional sequencing since it can sequence almost all mutations for thousands of genes. To make using NGS in cancer management easier, some challenges still exist. Improvements could include improving data throughput and analyzing and interpreting data more efficiently. The MRD in MM has been determined using NGS. It was crucial to establish Myeloma mutational heterogeneity, demonstrated by the range of altered genes and subclonal tumors. This supported creating case-specific and tailored treatment strategies for MM patients [70, 71]. There is a promising area of research involving cutting-edge methodologies for next-generation biomarkers which has the potential to contribute significantly to the diagnosis, prognosis, and treatment of multiple myeloma.

c) Liquid or Blood Biopsy

Because of the growing importance of CTCs and cfDNA in the diagnosis and prognosis of MM, liquid biopsy is used to capture these biomarkers from the peripheral circulation. Compared to BM Biopsy, it provides a potentially new minimally invasive ap-

proach for identifying disease stages and progression. Although BM biopsy is frequently carried out in MM cases, it still represents a burden due to the excruciating pain, tissue damage, and potential biopsy errors that relate to it, making it inapplicable for routine use for accurate assessment and continuous and proper disease monitoring [72]. Moreover, a liquid biopsy is less invasive and may be performed more frequently, which may help to explain why a single BM biopsy can miss MM clonal heterogeneity.

Diagnosis/prognosis of MM

It is the second most common hematologic malignancy in the United States and is caused by malignant monoclonal plasma cells proliferating uncontrollably in the bone marrow [73]. There are 12,830 fatal cases and 32,270 new cases of MM expected in 2020, with males, African Americans, and those aged 65 to 74 making up the majority of diagnoses (2013–2017). As of 2016, the median age at death for myeloma was 75 years (2010–2016), with a 5-year relative survival rate of 3.9 % [74]. Practitioners need to distinguish MM from other plasma cell neoplasms/dyscrasias. Besides psychosocial assessment, that is just the start of the diagnostic process. A complete blood count, peripheral blood smear, blood urea nitrogen, creatinine clearance, serum electrolytes, liver function tests, serum calcium, albumin, lactate dehydrogenase, and β 2-microglobulin are recommended by the National Comprehensive Cancer Network (NCCN) to determine whether a patient has symptomatic MM [75].

The importance of diagnostic tool development and use in MM control is rising. Diseases may be detected and predicted using various biomarkers today [76]. Diagnosing MM requires testing for free light chain (FLC) in the patient's blood and urine, as well as evaluating the number of monoclonal proteins (M proteins) and aberrant immunoglobulins (Igs) generated by malignant PCs. Patients with MM need to be categorized according to risk, which requires the discovery of chromosomal abnormalities and osteolytic bone lesions. To better treat patients, it is recommended to distinguish between the asymptomatic early stages of the disease and the symptomatic late stages. Blood or urine M protein concentrations and calcium, hemoglobin (Hb), and creatinine levels were used as diagnostic biomarkers in this study [16]. The Durie-Salmon PLUS Staging System (DSS) and the updated International Staging System for Multiple Myeloma (IMS-R) are two additional criteria for MM staging that have been (ISS). Both the DSS and the ISS are used to categorize MM's beginning and development, which is necessary for identifying the optimal treatment approach and determining a patient's median survival time. Several biomarkers in the blood or urine, in addition to chromosomal abnormalities, are the mainstays of these staging approaches [77]. Several new medications are being developed to treat multiple myeloma, and the prognosis is improving. However, the fact remains that multiple myeloma is a

chronic disease and requires lifetime care for patients. The prognosis of multiple myeloma varies based on numerous factors, but individuals who are treated well and who have an early-stage form of multiple myeloma are likely to have a favorable outcome.

Conclusion

Multiple myeloma, the most common blood cancer is incurable. Despite treatment and survival advances, high-risk patients have dismal survival rates. Because of this, proper identification of this group of patients has shown to be essential in improving patient outcomes. There is still a lot of interest and development in clarifying biomarkers that help in prognosis for MM patients, with the move towards precision treatment and patient management. An integrated strategy including clinical, genetic, imaging, serological, and protein biomarkers may be needed to guide medication selection and prognostication. Immune markers are becoming more critical for cancer detection and treatment. MM biomarkers are also being researched using proteomics and genomics; however, these findings must be validated before they can be employed in healthcare environments. Multiple myeloma can be diagnosed, monitored, and treated with these biomarkers. Combining these biomarkers with other clinical and laboratory tests allows medics to diagnose multiple myeloma and evaluate its treatment effectiveness more accurately. Monitoring these biomarkers can also help clinicians track the progress of this disease and adjust treatment accordingly.

In the realm of multiple myeloma treatment, the integration of modern biomarkers offers a transformative approach with far-reaching benefits. By delving into the intricate molecular and genetic facets of each patient's disease, biomarkers empower oncologists to tailor treatments with pinpoint precision. This personalized strategy not only enhances treatment efficacy but also mitigates unnecessary exposure to potentially ineffective therapies. Beyond this, biomarkers serve as

vigilant sentinels, allowing early diagnosis of illness development and supporting rapid alterations in treatment options. With insights into disease aggressiveness and prognosis, biomarkers empower informed decisions on treatment intensity and duration. They also act as discerning evaluators, guiding response assessments and therapeutic modifications. By minimizing toxicity and side effects, biomarker-guided treatments enhance patient well-being. Importantly, this paradigm amplifies clinical trial efficiency, enlightening optimal patient subgroups for targeted interventions. Furthermore, biomarkers foster patient engagement and resource optimization, while perpetuating a cycle of research, discovery, and innovation for the betterment of multiple myeloma care. Though modern biomarkers are still in their early stages of development, they can currently be used in the treatment of MM with significant benefits. A more precise and personalized prediction of therapeutic outcomes may be possible with modern biomarkers in MM patients. Current biomarkers are being used more and more in the treatment of MM. How these indicators can be used to improve patient outcomes are likely to become clearer with further research.

Abbreviations:

MM – Multiple Myeloma; B.M. – Bone Marrow; PCs – Plasma cells; MGUS – Monoclonal gammopathy of undetermined significance; SMM – Smouldering multiple Myeloma; O.S. – Overall survival; TNF- α – Tumour necrosis Factor-alpha; MDR1 – Multidrug resistance 1; MTHFR – Methylene tetrahydrofolate reductase; PCL – Plasma cell leukemia; BMM – Bone marrow microenvironment; ISS – International staging system; FISH – Fluorescent *in situ* hybridization; Ig – Immunoglobulin; VEGF – Vascular endothelial growth factor; FGF – Fibroblast growth factor; HGF – Hepatocyte growth factor; Ang-1 – Angioproten-1; Ang-2 – Angioproten-2; Treg – T-regulator; N.K. – Natural killer cells.

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Ramakrishnan Veerabathiran: designed the study, corrected the manuscript for submission.

Iyashwarya Bhaskar Kalarani: have written the contents.

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