

Experience of the hematology laboratory at avicenne hospital in Marrakech in the diagnosis and management of multiple Myeloma

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Abstract

Background: Multiple myeloma is a malignant hematologic disorder marked by clonal proliferation of plasma cells in the bone marrow, leading to overproduction of monoclonal immunoglobulins. This disease is frequently associated with serious complications, including osteolytic bone lesions, hypercalcemia, anemia, and renal failure.

Methods: This retrospective study reviews the clinical and biological profiles of patients with multiple myeloma diagnosed at the Hematology Laboratory of Avicenna Hospital in Marrakech. Molecular and cytogenetic biomarkers were integrated into the diagnostic strategy using advanced techniques such as next-generation sequencing (NGS) and mass spectrometry.

Results: Among 120 patients studied, recurrent mutations in KRAS, NRAS, and TP53 were identified. These genetic abnormalities had a significant impact on treatment response and prognosis. Patients with TP53 mutations had poorer outcomes, while those with KRAS/NRAS mutations showed better progression-free survival (PFS). Autologous stem cell transplantation and the use of novel agents, including proteasome inhibitors and BCMA-targeted therapies, improved survival outcomes.

Conclusions: The integration of molecular and cytogenetic profiling into routine diagnostic practice enhances the stratification and individualized treatment of multiple myeloma. The study underscores the clinical benefits of targeted therapies while highlighting the ongoing challenges of therapeutic resistance and access disparities.

Keywords: Multiple Myeloma; Plasma Cells; Cytogenetics; Targeted Therapy

1. Introduction

Multiple myeloma (MM) is a malignant hematologic disorder characterized by the clonal proliferation of plasma cells within the bone marrow. This expansion is accompanied by the excessive and abnormal production of monoclonal immunoglobulins, leading to major clinical complications including osteolytic bone lesions, hypercalcemia, anemia, and renal insufficiency. MM accounts for approximately 10% of all hematologic malignancies and predominantly affects older adults, with a median age at diagnosis of around 70 years [1,2].

Recent advances in molecular biology have significantly transformed the diagnosis and risk stratification of MM. The integration of biomarkers, including mutations in KRAS (Kirsten Rat Sarcoma viral oncogene homolog), NRAS (Neuroblastoma RAS viral oncogene homolog), and TP53 (Tumor Protein 53), as well as the use of next-generation sequencing (NGS), allows for more refined patient classification and the personalization of therapeutic strategies [3]. Additionally, technologies such as mass spectrometry and cytogenetic tools have proven critical in identifying complex chromosomal abnormalities that are often associated with poor prognosis [4].

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This study presents the experience of the Hematology Laboratory at Avicenna Hospital in Marrakech in implementing these technologies to improve risk stratification, treatment monitoring, and clinical outcomes in patients with MM.

2. Patients and Methods

This retrospective study included patients diagnosed with multiple myeloma (MM) between January 2015 and December 2021 at the Hematology Laboratory of Avicenna Hospital in Marrakech, Morocco. Medical records were reviewed to extract clinical data (initial presentation, systemic involvement) and biological data (cytogenetic results, molecular analyses, and serum monoclonal immunoglobulin levels).

2.1. Diagnostic Techniques

- **Conventional Cytogenetics:** Performed on bone marrow samples to detect chromosomal abnormalities such as deletions and translocations.
- **Next-Generation Sequencing (NGS):** Used to identify mutations in *KRAS*, *NRAS*, and *TP53* genes. Analyses were conducted on DNA extracted from tumor cells.
- **Proteomic Analysis:** Conducted via mass spectrometry to quantify monoclonal immunoglobulins.

2.2. Inclusion Criteria

- Confirmed diagnosis of MM based on International Myeloma Working Group (IMWG) criteria.
- Availability of complete cytogenetic and molecular profiles.
- Documented clinical follow-up for a minimum of 24 months.

2.3. Exclusion Criteria

- Presence of concurrent malignant disorders.
- Incomplete cytogenetic or molecular data.

2.3.1. Statistical Analysis

Data were analyzed using SPSS version 25.0. Quantitative variables were expressed as means $\pm$ standard deviation, and qualitative variables as percentages. Statistical significance was defined as $p < 0.05$. Survival curves were estimated using the Kaplan–Meier method.

3. Results

A total of 120 patients with multiple myeloma were included in the study. The mean age was 64.3 ± 10.2 years, with a male predominance (58%). At diagnosis, 85% of patients presented with osteolytic bone lesions, and 42% had renal insufficiency.

3.1. Cytogenetic and Molecular Findings

- The most common cytogenetic abnormalities were deletion of 13q (35%) and immunoglobulin heavy chain (IGH) translocations (25%).
- NGS identified recurrent mutations in *KRAS* (22%), *NRAS* (18%), and *TP53* (10%).
- Patients harboring co-mutations had significantly poorer prognoses.

3.2. Age-Based Outcome Disparities

Patients aged over 70 years experienced significantly shorter progression-free survival (PFS), with a median of 22 months compared to 36 months in younger patients.

3.3. Treatment Responses

- Patients treated with proteasome inhibitors (bortezomib or carfilzomib) demonstrated high response rates:
 - 35% achieved stringent complete response (sCR)
 - 30% achieved very good partial response (VGPR)

3.4. Impact of Genetic Mutations on Survival

- *TP53* mutations were strongly associated with treatment resistance and reduced median overall survival (24 months).
- Conversely, patients with *KRAS* or *NRAS* mutations had significantly longer PFS (36 months).

3.5. Autologous Stem Cell Transplantation

- 48% of patients underwent autologous stem cell transplantation (ASCT), resulting in substantial clinical benefits.
- In the transplant group, both overall and progression-free survival improved significantly ($p < 0.001$).

3.6. Genetic Complexity and Treatment Outcome

- Patients with multiple cytogenetic abnormalities (e.g., 13q deletion + IGH translocation) had inferior responses and faster progression.
- In contrast, those with isolated abnormalities exhibited better outcomes ($p = 0.04$).

3.7. Targeted Therapies

- Subgroups receiving combination regimens that included novel targeted agents—especially BCMA (B-cell maturation antigen) inhibitors—achieved the most favorable outcomes.
- In this group, median PFS extended to 42 months.

4. Discussion

The findings of this study underscore the pivotal role of molecular diagnostics and advanced analytic tools in characterizing the genetic landscape of multiple myeloma (MM). The prevalence of *KRAS* and *NRAS* mutations aligns with previous reports identifying their potential utility as predictive biomarkers for favorable treatment responses. A recent 2023 study demonstrated that *KRAS* mutations activate distinct intracellular signaling pathways, which may explain their increased sensitivity to targeted agents [5].

In contrast, *TP53* abnormalities—though less common—present significant diagnostic and therapeutic challenges. These mutations are often associated with high-risk disease, early relapse, and resistance to conventional therapies, consistent with recent literature [6].

4.1. Efficacy of Proteasome Inhibitor-Based Regimens

The use of proteasome inhibitors (bortezomib or carfilzomib) yielded a 35% complete response rate, mirroring international data [7]. Furthermore, phase III clinical trials have shown that combining daratumumab with standard regimens significantly improves stringent complete response and progression-free survival, particularly in high-risk subgroups [8].

4.2. Role of Biomarker-Driven Stratification

Stratification based on genomic profiling has proven essential for tailoring therapy. A 2023 systematic review highlighted the prognostic value of BCMA (B-cell maturation antigen) as a therapeutic target, enabling more personalized and less toxic regimens [9]. Agents targeting BCMA—such as belantamab mafatotin—have shown promising efficacy in refractory disease, offering hope for patients with otherwise limited treatment options.

4.3. Persistent Challenges in High-Risk Subgroups

Despite these advances, treatment of patients with *TP53* mutations or complex co-mutations remains suboptimal. These individuals often demonstrate primary resistance to both proteasome inhibitors and immunomodulatory agents. Additionally, cumulative toxicity, especially in older or frail patients, restricts the prolonged use of certain regimens. A 2022 study highlighted the hematologic and renal toxicities associated with proteasome inhibitors as a limiting factor in long-term disease control [10].

Among patients over 70 years, median PFS was significantly reduced (22 vs. 36 months), consistent with age-related declines in treatment tolerance and comorbidity burden [4]. While autologous stem cell transplantation (ASCT) provided substantial clinical benefit, eligibility criteria—often restricted by age or comorbidities—exclude a large subset of patients.

4.4. Diagnostic Technology and Limitations

Advancements in next-generation sequencing (NGS) have revolutionized mutation profiling, allowing for detection of sub clonal and low-frequency variants. Platforms that target *KRAS* and *TP53* mutations provide enhanced sensitivity and are vital for tracking clonal evolution in MM [11]. However, the high cost and infrastructural demands of NGS limit its availability in many low-resource settings.

Mass spectrometry has emerged as a superior tool for quantifying free light chains and monoclonal proteins. Although it offers greater specificity compared to traditional assays, inter-laboratory variability remains a concern, warranting standardization [12].

Flow cytometry remains essential for phenotyping malignant plasma cells but is constrained by limited access to reagents for emerging markets such as BCMA and the high cost of multiparametric platforms. Moreover, the interpretation of flow cytometry data requires advanced technical expertise [13].

4.5. Therapeutic Insights and Access Barriers

Patients harboring isolated *KRAS* mutations appeared to benefit most from BCMA-targeted therapies, with a median PFS of 42 months. Conversely, those with multiple cytogenetic abnormalities require integrated strategies combining novel targeted therapies with maintenance approaches to overcome resistance mechanisms.

Global disparities in access to innovative therapies—especially monoclonal antibodies and BCMA inhibitors—pose significant challenges. High costs and logistic hurdles impede widespread adoption in many regions. A 2023 review further highlighted the lack of standardized protocols for managing heavily pretreated or refractory disease, emphasizing the urgent need for new therapeutic strategies [10].

Finally, while ASCT remains effective in eligible patients, its integration into genomics- and proteomics-informed treatment algorithms is still evolving. Emerging data suggest that molecular profiling may guide transplant candidacy and predict long-term outcomes, particularly when combined with targeted maintenance agents [7]. These insights reinforce the need for ongoing research into less toxic; more accessible therapies tailored to an increasingly heterogeneous patient population..

5. Conclusion

This study highlights the critical value of an integrated approach combining technological innovation and molecular biomarkers in the comprehensive management of multiple myeloma. The incorporation of advanced diagnostic techniques—such as next-generation sequencing, cytogenetics, and proteomics—has enhanced the precision of risk stratification and informed individualized treatment decisions.

Our findings emphasize the prognostic relevance of genetic mutations, particularly *TP53*, *KRAS*, and *NRAS*, in guiding therapeutic choices and predicting clinical outcomes. Furthermore, the demonstrated efficacy of targeted therapies, including proteasome inhibitors and BCMA-directed agents, underscores their central role in modern myeloma care.

Future research should prioritize the development of personalized treatment strategies for high-risk patients, especially those with complex genomic profiles or co-mutations. Additionally, expanding global access to novel therapies and ensuring equitable care delivery must remain a strategic priority.

Ultimately, optimizing survival and quality of life in multiple myeloma will depend on continued advances in translational research, international collaboration, and the implementation of biomarker-driven, patient-centered care.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Avicenne Hospital, Marrakech, Morocco.

Statement of informed consent

Written informed consent was obtained from all participants following a clear explanation of the study's objectives

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