Review

Myeloma Genetics and Genomics: Practice Implications and Future Directions

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Abstract

Multiple myeloma (MM) is a heterogeneous, clonal disorder of the plasma cells originating from the B-cell line. The diagnosis and monitoring of MM requires routine measurement of biomarkers such as serum protein electrophoresis, urine protein electrophoresis, serum free light chains, among others. Prognostic models such as the Durie-Salmon staging system and International Staging System are available and account for the disease burden. Advanced biomarker and genetic testing includes cytogenetics, fluorescent in situ hybridization, and gene expression profiling to estimate the aggressiveness of the disease and personalize the patient's treatment. Future goals of therapy will be to achieve minimal residual disease (MRD), which incorporates biomarkers and genomic data. MRD testing might provide a better estimate of the depth of response to therapy and overall survival. A robust genomic program of research is still needed to provide additional information for the best MM care practices and to gain new strategies to treat the disease, in particular, in the relapsed and/or refractory setting.

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Biomarker Discovery in Multiple Myeloma: A Historical Perspective

Biomarkers are integral to the diagnosis and management of diseases, such as cardiovascular disease, diabetes, and cancers such as multiple myeloma (MM). A biomarker is defined as a characteristic that can be objectively measured to diagnose the disease, determine its response to medications, and/or estimate the prognosis.[1] In 2014, biomarker discovery has been abundant, but its significance in MM was first recognized in the 19th century.

In 1845, a 45-year-old tradesman named Thomas Alexander Bean had a role in the discovery of the first biomarker known to diagnose MM: Bence Jones proteins.[2] Over a period of time, Mr. Bean had experienced fatigue and changes in urination. His urine was sent to Dr. Henry Bence Jones, who examined the heat properties of the urinary proteins in the specimen. From the findings of the abnormal urinary proteins, Mr. Bean received treatment with steel and quinine. Despite a short remission, he died of the illness known today as MM.[2]

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Science progressed with the discovery of new methods to measure and treat MM. In 1898, Dr. Wright determined that MM arose from the plasma cells.[3] The bone marrow aspiration technique followed in 1927, when Peabody [4] described the bone marrow histologic features in pernicious anemia. Tiselius[5] reported preliminary work on the properties of serum globulins in 1937. Alkeran in 1958 and prednisone in 1962 were among the first agents to effectively treat MM according to the clinical evidence of the disease.[6]

Fast forward to the last quarter of the 20th century. Insight into oncogenes, pro-oncogenes, and the complex genetic biology of cancers in the 1970s led the groundwork for drug discovery and targeted agents.[7] Today, patients with MM have access to newer classes of agents with sophisticated mechanisms of action. Drugs approved by the U.S. Food and Drug Administration include the proteasome inhibitors bortezomib (2003)[8] and carfilzomib (2012)[9] and the immunomodulatory drugs thalidomide (2006),[10] lenalidomide (2006),[11] and pomalidomide (2013).[12] Other emerging agents with unique targets are currently in clinical trials and include elotuzumab, daratumumab, oprozomib, and ixazomib, among others.[13-16]

Biomarkers in MM

Biomarkers Commonly Used for Diagnosis

The diagnosis of MM is made using the International Myeloma Working Group (IMWG) criteria. The IMWG determined that patients must have a detectable monoclonal protein in the serum or

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urine, > 10% clonal bone marrow plasma cells, and 1 site of MM-related end-organ dysfunction. The organ dysfunction can be recalled using the "CRAB pneumonic": hypercalcemia (> 11.5 mg/L or upper limit of normal), renal insufficiency (serum creatinine > 2 mg/dL), anemia (hemoglobin < 10 g/dL or 2 g less than normal), or bone disease (Table 1).[17,18]

Biomarkers Commonly Used for Staging

Two staging systems for MM exist for prognosis: the Durie-Salmon staging system (DS) and the International Staging System (ISS). The DS staging system was first described in 1975 and accounts for disease burden and the degree of end-organ damage caused by the MM.[19] The amount of paraprotein elevation and degree of anemia, renal insufficiency, and bone damage related to the MM is also considered.[19]

The ISS was first reported in 2005. Data were used from an international sample of 10,750 patients with newly diagnosed MM before initial therapy.[20] Multiple demographic and laboratory parameters were evaluated in all patients within the 30 days before the initiation of systemic therapy. Univariate and multivariate analyses established 2 important biomarker tests, the serum albumin and β2-microglobulin tests, as reliable prognostic predictors of overall survival, regardless of age, treatment type, or geographic location. In 2011, the ISS was evaluated in patients with renal insufficiency and has remained a reliable prognostic predictor in patients with renal dysfunction.[21] Both the DS and the ISS systems provide accurate staging for MM. Future staging systems should account for tumor genetics to better assess the disease burden (Table 2).

Genomic Tests as Advanced MM Biomarkers

B-Cell Development and Genetics in MM

To understand the genetic changes in MM, one must be familiar with the role of immunoglobulin (Ig) development. Lymphocytes differentiate into T (thymus) cells and B (bone marrow-derived) cells. B lymphocytes produce a multitude of clonally diverse immunoglobulins.[22] The main role of immunoglobulins is to recognize foreign antigens and generate an appropriate immune response.[23]

Table 1 Criteria for Diagnosis of Symptomatic MM

Abnormality	Result
Calcium elevation	Hypercalcemia (serum calcium ≥11.5 mg/dL) OR
Renal insufficiency	Serum creatinine >2.0 mg/dL OR
Anemia	Hemoglobin >2 g/100 mL less than the lower limit of normal OR hemoglobin value <10 g/100 mL OR
Bone	Lytic lesions, widespread osteoporosis, or pathologic fractures on skeletal survey, PET-CT, or MRI

To qualify for a MM diagnosis, patients must have clonal bone plasma cells or plasmacytoma and organ damage related to the paraprotein.
Abbreviations: MM = multiple myeloma; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography.
Data from BGM Durie, J-L Harousseau, JS et al. on behalf of the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia (2006), 1-7 and Dimopolous et al International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia (2009), 1-12.

Table 2 Comparison of International Staging System and Durie-Salmon Staging System

ISS Stage	Description	DSS Stage	Description
Stage I	Serum β2-microglobulin <3.5 mg/L and serum albumin ≥3.5 g/dL	Stage I	All of the following: hemoglobin >10g/dL; serum calcium normal or <10.5 mg/dL; bone radiograph showing normal bone structure (scale 0) or solitary bone plasmacytoma only; low M-component production rate (IgG <5 g/dL; IgA <3 g/dL); urine light chain M-component on electrophoresis <4 g/24 h
Stage II	Not stage I or III	Stage II	Not stage I or II
Stage III	Serum β2-microglobulin ≥5.5 g/dL	Stage III	One or more of the following: hemoglobin <8.5 g/dL; serum calcium >12 mg/dL; advanced lytic bone disease; high M-component production rate (IgG >7 g/dL; IgA >5 g/dL); Bence Jones protein >12 g/24 h
		Substage	A: serum creatinine <2 mg/dL B: serum creatinine >2 mg/dL

Abbreviations: DSS = Durie-Salmon staging; Ig = immunoglobulin; ISS = International Staging System; M = monoclonal.
Data from Durie BG, Salmon SE. A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. Cancer *1975; 36:842-54 and from Greipp PR, et al. International staging system for multiple myeloma.* J Clin Oncol *2005; 23:3412-20.*

Ordered and functional Ig loci rearrangements play an active role in B-cell development.[22] Ig molecules are composed of heavy chain (IgG, IgA, IgM, IgD, and IgE) and light chain (κ and λ) proteins. The Ig locus contains 4 segments: V (variable), D (diversity), J (joining), and C (constant). V-D-J recombination occurs early on in B-cell development, creating an Ig heavy (IgH) chain rearrangement (VDJ_H), which is then followed by a V-J recombination that affects the light chain loci (VJ_L).[22,24] Because the IgH rearrangement occurs early in B-cell development, this specific genetic change is an early marker of clonal B-lymphoid cell populations. Through a complex series of cellular genetic changes, mutations, and alterations, clonal populations will emerge.[25]

An essential method to determine the disease extent and characteristics of the MM tumor is bone marrow biopsy.[18,26] Chromosomal aberrations in MM will be observed using bone marrow cytogenetic (karyotype) analysis and fluorescent in situ hybridization (FISH) testing.[25,27,28] When a bone marrow biopsy is performed, immunostains will reveal clonal κ- or λ-restricted plasma cells positive for the main plasma cell markers (CD38 and CD138). Cytogenetics testing can also be performed using liquid bone marrow aspirate. The cells are then cultured. After a 48- to 96-hour culture period, chromosomes in the metaphase of development are harvested and analyzed.[29,30]

In addition to cytogenetic testing, FISH analysis can be used to further determine the prognosis and lead treatment decision-making using FISH tests for specific IgH translocations on liquid bone marrow aspirate of monoclonal plasma cells. Cytogenetics and FISH tests are performed using clonal plasma cells to reflect the tumor