The Changing Face of Multiple Myeloma

Sikander Ailawadhi, MD

Abstract

Our understanding of multiple myeloma, including its pathophysiology, clinical behavior, and management, has improved immensely over recent years. This has translated into development of a more diverse portfolio of therapeutic agents and significantly improved patient outcomes, with the survival among standard-risk patients being in the vicinity of 10 years or more. This also has led to redefining some of the basic concepts surrounding this diagnosis, including the definition of multiple myeloma, response criteria, risk stratification, and goals of treatment. This article reviews some of these concepts that are still evolving and are thus shaping how we see and manage multiple myeloma—hopefully moving slowly but surely toward its elusive cure.

Key words: multiple myeloma, International Myeloma Working Group, risk stratification

It is frequently mentioned that the outcomes of patients with multiple myeloma are ever improving, mostly due to the advent of "novel therapeutic agents." It is notable that less than 15 years ago, diagnosis of multiple myeloma carried a dismal prognosis with no drugs specifically approved by the FDA for its treatment. Since then, not just the therapeutic agents—many of which don't seem novel anymore—but our understanding of various other aspects of this disease including its pathophysiology and diagnostic and prognostic techniques, have evolved immensely. The goal of this review is to highlight some of these landmark changes that have modified the way we see multiple myeloma and discuss others that are still evolving and that will surely impact the future of patients with this disease, which is so far considered incurable by most (**Table 1**).

Redefining Multiple Myeloma

Although, historically, the definition of *active multiple myeloma* required treatment to be initiated at the first sign of end-organ damage (per the CRAB criteria),[1] the majority of the patients did not receive treatment to prevent this damage from setting in. This may have been acceptable when the therapeutic options were limited and there was no apparent benefit from early intervention, but in an era when 5-year survival from myeloma is quoted at approximately 50%[2] and some patients are living with this disease for 10 years or longer, the need to prevent end-organ damage rather than merely treating it has become imperative in ensuring improved survivorship and better tolerability to subsequent therapies.

Considering this, the International Myeloma Working Group (IMWG) recently updated its definition of *active multiple myeloma* by adding cases that do not meet the classic CRAB criteria, but that have clonal bone marrow plasma cell percentage ≥60%, an involved:uninvolved serum free light-chain ratio ≥100 with the involved serum free light-chain ≥10 mg/dL, or more than 1 focal lesion on magnetic resonance imaging (MRI) studies.[3] Furthermore, the widespread utilization and availability of serum and urine free light-chain analyses has decreased the number of truly nonsecretory cases of multiple myeloma, providing measurable markers of disease assessment and response in a larger number of patients. It is also accepted that patients with a biopsy-proven bony or extramedullary plasmacytoma and meeting any of the CRAB criteria, even without ≥10% clonal bone marrow plasma cells, are treated as active myeloma.[3] While all of this certainly will increase the prevalence of active multiple myeloma, it also will affect clinical trial eligibility and outcomes by introducing a subgroup of patients to treatment before the morbidity from the diagnosis affects them.

Understanding Multiple Myeloma Pathophysiology

Our understanding of the pathophysiology of multiple myeloma has gone beyond the traditional view of it as a malignant monoclonal plasma cell disorder that eventually becomes refractory to treatment. With genomic and epigenetic analyses, a clearer picture is emerging of the various factors at play as the disease course progresses. Studies consistently show that in every patient with multiple myeloma, several parallel malignant clones are present at the time of diagnosis, with the clonal characteris-

tics changing over time and in relation to therapy.[4] In patients known to have high-risk disease by cytogenetics, significantly more genomic changes occur over time compared with patients with standard-risk myeloma, suggesting genetic instability in the former.[4] Thus, while effective treatment may reduce or eliminate the dominant clone, other clones can still exist and gain a survival and/or growth advantage. This may provide a basis for the deeper and more durable responses being seen with combination regimens in the frontline as well as the relapsed myeloma setting.[5,6]

Several reports over the past few years have focused on the interaction of genetic alterations in multiple myeloma with epigenetic changes, such as aberrant DNA and histone methylation or abnormal microRNA expression that are found to contribute to the pathobiology of the disease.[7-9] The interaction of the malignant clone with its microenvironment, as well as mechanisms that lead to the malignant plasma cell evading such interactions in advanced disease, is also being better understood, leading to the development of newer, distinct classes of drugs.[10]

Risk Stratification

Once a patient with multiple myeloma meets the criteria for receiving treatment, risk stratification is conducted to discuss and determine prognosis, even potential treatment strategies. Whereas patient characteristics such as age,[11] performance status, and disease stage[12] are important considerations, nearly every patient is risk-stratified by looking for mutations using fluorescence in-situ hybridization or conventional karyotyping.[13,14] Beyond defining average outcomes in patients with newly diagnosed multiple myeloma, it was speculated that the cytogenetic risk categories may be used to guide the choice of therapeutic regimen as well as the duration of therapy.[15] However, data from recent studies show that multiple myeloma patients with standard-risk biology are the ones who are benefiting most from highly effective novel regimens,[6,16] whereas effective therapies for patients with higher-risk biology are yet to be better defined. The mutations included in various risk categories of multiple myeloma have also changed over time.[17-19] Although the role of cytogenetics in determining the prognosis of patients with is well established and is the basis for several guidelines and clinical trials, newer technologies exploring genomic variability of the malignant clone, utilizing gene expression profiling, have become available in recent years. These include myPRS, SKY-92,[20,21] and M^{3}P,[22,23] which provide a prognostic framework defining patient subgroups and their expected clinical behavior, as well as long-term outcomes.

Use of Molecular Data to Determine Treatment Choices

The role of biologic characteristics of the plasma cell beyond risk stratification in determining therapeutic options is emerging. Mutations in the cereblon gene leading to lower expression have been associated with resistance to immunomodulatory drugs (IMiDs) and poorer response rates and overall survival (OS) in patients treated with pomalidomide.[24] This may seem to be the first biomarker in multiple myeloma with therapeutic implications, but it is not yet being used in routine practice. More standardization and calibration is needed before this may be widely available and used to direct therapeutic choices in routine patient care. Similar biomarkers, which may be helpful in predicting a response to proteasome inhibitor treatment in patients with multiple myeloma are *IRE1/XBP1*, the suppression of which confers resistance to bortezomib, although this has only been reported mostly in preclinical models with sparse patient-level data.[25]

Another group of biomarkers being tested to determine therapeutic eligibility is the expression of surface antigens on plasma cells, against which monoclonal antibodies (mAbs) are in clinical development (eg, CD38, CD138, CD56). One of the tools that should be available soon for commercial use is a molecular profiling panel called MMprofiler (SkylineDx), which would have the capability of providing the SKY92 prognostic gene signature, cytogenetic markers, GEP clusters, single-gene expression, and patient-level customized genome-wide data.

TABLE 1. Redefining Diagnosis and Management of Multiple Myeloma

Feature	Update
Diagnostic criteria for multiple myeloma	End-organ damage no longer required to treat
Advanced imaging techniques for workup	Skeletal survey on the way out
Pathophysiology	Clonal evolution and competition supports multiagent regimens
Multiagent combination therapy	For all risk categories to optimize outcomes
Response assessment with newer combination regimens	Development of MRD monitoring
MRD negativity	Consistently associated with longer progression-free and overall survival

MRD indicates minimal residual disease.

Updating the Response Criteria

From 1998 until 2006, the clinical responses in patients with multiple myeloma, as well as determining disease relapse, were based on the European Group for Blood and Marrow Transplantation criteria.[26] The IMWG updated these criteria in 2006, when some older definitions were clarified, new response categories were added, and the free light-chain criteria for measurable disease and response were defined.[27,28] This update went beyond just a state of complete response (CR) to further categorize it into mo-

lecular CR, immunophenotypic CR, and stringent CR.[27] These refinements of the CR category have been validated in various clinical settings and are achievable therapeutic goals to improve patient outcomes.[29] Because the recently reported and currently used treatment regimens for multiple myeloma have been showing better responses than ever noted before, there has been work to further refine the depth of response by determining minimal residual disease (MRD) status of patients. This can be done by utilizing flow cytometry or high-throughput sequencing. Studies have shown that among patients achieving a biochemical CR, MRD-negative status is associated with superior outcomes, including progression-free survival (PFS) and OS.[30-32] Recent data show that high-throughput sequencing–based MRD testing has at least a 10-fold higher sensitivity than the flow cytometry–based methodology.[16] These techniques are being employed commonly in clinical trials, but uniform criteria for routine clinical practice are yet to be established.

Another aspect of the change has been the newer imaging modalities, of which positron emission tomography (PET) and MRI scans have been included in disease assessment and progression criteria already, as as well as the IMWG and are now considered standard of care.[3] Further refinement of these techniques has helped in predicting prognosis in various therapeutic settings. For example, the presence of more than 3 focal lesions or standardized uptake value >4.2 at diagnosis are predictors of shorter PFS, and PET-CT negativity 3 months after an autologous stem cell transplant (ASCT) predicts a superior PFS and OS.[33]

TABLE 2. Selected Modern Multiple Myeloma Therapies, Available and in Development

Drug Category	Agent
Proteasome inhibitor	Bortezomib Carfilzomib Ixazomib Oprozomib
Immunomodulatory agent	Thalidomide Lenalidomide Pomalidomide
Histone-deacetylase inhibitor	Panobinostat
Monoclonal antibody	Daratumumab and SAR650984 (anti-CD38) Elotuzumab (anti-CS1), BT062 (anti-CD138) BB10901 (anti-CD56)
Kinesin spindle protein inhibitor	Filanesib
PI3K-AKT-mTOR inhibitor	Afuresertib
PIM-kinase inhibitor	LGH447
Nuclear protein exportin 1	Selinexor
Chimeric antigen receptor T cells	
Vaccine therapy	

Shifting Goals of Multiple Myeloma Treatment

Historically, the treatment algorithm guidelines in multiple myeloma have been based on whether a patient is considered ASCT-eligible or not. This had dichotomized the treatment approach, with the major difference being that younger, transplant-eligible patients would not be given melphalan-based regimens.[19] Although this is still true, the distinction between transplant-eligible and -ineligible patients become less defined in recent years. The combination therapeutic regimens being used widely with IMiDs and proteasome inhibitors, such as cyclophosphamide-bortezomib-dexamethasone, lenalidomide-bortezomib-dexamethasone, and carfilzomib-lenalidomide-dexamethoasone, are fairly well tolerated and have made the use of melphalan less frequent, at least in the United States.[6,34]

Since the response rates have been ever improving, achieving an objective response to induction treatment in nearly all patients has become the norm rather than the exception, at least in the newly diagnosed setting and in a significant proportion of patients with relapsed disease. Thus, the comparator arm in randomized, phase III clinical trials is no longer single-agent dexamethasone alone and novel combination regimens have to show further improvement over the benefit from IMiD and proteasome inhibitor–containing doublets—at the least. The goals of treatment and therapeutic decision making have, in turn, been broadened to address several previously overlooked questions, such as quality of life, survivorship, improving depth of response, managing long-term complications, refining the duration of treatment, and demonstrating improvement in OS.[35-37]

The Era of Real Novel Therapeutic Agents

The first novel therapeutic agent for the treatment of multiple myeloma to be approved by the FDA was bortezomib in 2003. Since then, the 2 classes of drugs, proteasome inhibitors and IMiDs, have defined how we manage this disease and have resulted in significantly improved OS and PFS in patients. However, until recently, the only newer agents receiving FDA approval for the treatment of myeloma were more drugs within these 2 classes, with better side-effect profiles and an improvement in efficacy.[38,39] In 2014, a novel category of targeted drugs, the histone-deacetylase inhibitors, became available, with panobinostat being the first agent in this category.[40] Although these agents have been received with some debate around its efficacy and adverse-event profile, several combination trials are under way to better define its role in myeloma therapeutics. Nevertheless, the availability of a novel drug class, rather than just novel agents

within the older classes, is an exciting development. Several more drug classes are undergoing rapid clinical development, including mAbs (eg, anti-CD38, anti-CD138, and anti-CS1), a kinesin spindle protein inhibitor (filanesib), a phosphatidylinositide-3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway inhibitor (afuresertib), a PIM-kinase inhibitor (LGH447), and a nuclear protein exportin 1 (selinexor), among others.[41] Alternative approaches, including vaccine therapy and chimeric antigen receptor (CAR) T cells, are also being explored for multiple myeloma in several ongoing clinical trials (**Table 2**).[42,43] Availability of these and other truly novel therapeutic options will help take the next step toward improving outcomes in patients with multiple myeloma by hopefully affecting disease biology and deepening the response rates, as well as providing more longer lasting efficacy, potentially realizing an elusive cure in this disease.

Affiliation: Sikander Ailawadhi, MD, is from the Division of Hematology-Oncology, Mayo Clinic, Jacksonville, FL.
Disclosure: Dr Ailawadhi has been a consultant and on the advisory board for Takeda Oncology and Onyx Pharmaceuticals.
Address correspondence to: Sikander Ailawadhi, MD, Division of Hematology-Oncology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32256. Phone: 904 953 6468; email: ailawadhi.sikander@mayo.edu

REFERENCES

1. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.
2. SEER cancer statistics factsheets: Myeloma. Bethesda, MD: National Cancer Institute.
3. 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):e538-548.
4. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5):1067-1076.
5. Kapoor P, Ramakrishnan V, Rajkumar SV. Bortezomib combination therapy in multiple myeloma. *Semin Hematol*. 2012;49(3):228-242.
6. Stewart AK, Rajkumar SV, Dimopoulos MA, et al; ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-152.
7. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471(7339):467-472.
8. Dimopoulos K, Gimsing P, Gronbaek K. Aberrant microRNA expression in multiple myeloma. *Eur J Haematol*. 2013;91(2):95-105.
9. Sharma A, Heuck CJ, Fazzari MJ, et al. DNA methylation alterations in multiple myeloma as a model for epigenetic changes in cancer. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2(6):654-669.
10. Ocio EM, Richardson PG, Rajkumar SV, et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). *Leukemia*. 2014;28(3):525-542.
11. Ailawadhi S, Aldoss IT, Yang D, et al. Outcome disparities in multiple myeloma: a SEER-based comparative analysis of ethnic subgroups. *Br J Haematol*. 2012;158(1):91-98.
12. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23(15):3412-3420.
13. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc*. 2007;82(3):323-341.
14. Stewart AK, Bergsagel PL, Greipp PR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia*. 2007;21(3):529-534.
15. Mikhael JR, Dingli D, Roy V, et al; Mayo Clinic. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-376.
16. Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol*. 2015;1(6):746-754.
17. An G, Xu Y, Shi L, et al. Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation and percentage of plasma cells involved have no additional prognostic value. *Haematologica*. 2014;99(2):353-359.
18. Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Oncol*. 2011;8(8):479-491.
19. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2012;87(1):78-88.
20. Kuiper R, Broyl A, de Knegt Y, et al. A gene expression signature for high-risk multiple myeloma. *Leukemia*. 2012;26(11):2406-2413.
21. van Laar R, Flinchum R, Brown N, et al. Translating a gene expression signature for multiple myeloma prognosis into a robust high-throughput assay for clinical use. *BMC Med Genomics*. 2014;7:25.
22. Kortum KM, Langer C, Monge J, et al. Targeted sequencing using a 47 gene multiple myeloma mutation panel (M(3) P) in -17p high risk disease. *Br J Haematol*. 2015;168(4):507-510.

23. Kortum KM, Langer C, Monge J, et al. Longitudinal analysis of 25 sequential sample-pairs using a custom multiple myeloma mutation sequencing panel (M(3)P). *Ann Hematol*. 2015;94(7):1205-1211.
24. Schuster SR, Kortuem KM, Zhu YX, et al. The clinical significance of cereblon expression in multiple myeloma. *Leuk Res*. 2014;38(1):23-28.
25. Leung-Hagesteijn C, Erdmann N, Cheung G, et al. Xbp1s-negative tumor B cells and pre-plasmablasts mediate therapeutic proteasome inhibitor resistance in multiple myeloma. *Cancer Cell*. 2013;24(3):289-304.
26. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102(5):1115-1123.
27. Durie BG, Harousseau JL, Miguel JS, et al; International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.
28. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia*. 2009;23(1):3-9.
29. Kapoor P, Kumar SK, Dispenzieri A, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. *J Clin Oncol*. 2013;31(36):4529-4535.
30. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood*. 2014;123(20):3073-3079.
31. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol*. 2013;31(20):2540-2547.
32. Mailankody S, Korde N, Lesokhin AM, et al. Minimal residual disease in multiple myeloma: bringing the bench to the bedside. *Nat Rev Clin Oncol*. 2015;12(5):286-295.
33. Zamagni E, Patriarca F, Nanni C, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. *Blood*. 2011;118(23):5989-5995.
34. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood*. 2012;119(19):4375-4382.
35. Ludwig H, Durie BG, McCarthy P, et al; International Myeloma Working Group IMWG consensus on maintenance therapy in multiple myeloma. *Blood*. 2012;119(13):3003-3015.
36. Sonneveld P, Verelst SG, Lewis P, et al. Review of health-related quality of life data in multiple myeloma patients treated with novel agents. *Leukemia*. 2013;27(10):1959-1969.
37. Bilotti E, Faiman BM, Richards TA, et al. Survivorship care guidelines for patients living with multiple myeloma: consensus statements of the International Myeloma Foundation Nurse Leadership Board. *Clin J Oncol Nurs*. 2011;15 (suppl:5-8).
38. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood*. 2012;120(14):2817-2825.
39. Elkinson S, McCormack PL. Pomalidomide: first global approval. *Drugs*. 2013;73(6):595-604.
40. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15(11):1195-1206.
41. Mimura N, Hideshima T, Anderson KC. Novel therapeutic strategies for multiple myeloma . *Exp Hematol*. 2015;43(8):732-41. doi: 10.1016/j.exphem.2015.04.010.
42. Garfall AL, Fraietta JA, Maus MV. Immunotherapy with chimeric antigen receptors for multiple myeloma. *Discov Med*. 2014;17(91):37-46.
43. Russell SJ, Federspiel MJ, Peng KW, et al. Remission of disseminated cancer after systemic oncolytic virotherapy. *Mayo Clin Proc*. 2014;89(7):926-933.