Review

High-Risk Multiple Myeloma: Different Definitions, Different Outcomes?

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Abstract

Multiple myeloma (MM) is a clonal plasma cell malignancy. Although MM is still not completely curable, it can be maintained at the level of a long-term chronic condition. Irrespective of the treatment strategy, relapse is still a major problem for most patients. Approximately 10% to 15% of all MM patients relapse early and have poor prognosis and outcome. Currently, there are many ways of identifying these high-risk patients using cytogenetics or molecular biology. Despite these various approaches to definition of high risk patients, a clear definition of high-risk MM has not been widely accepted. In this review, we discuss and compare various approaches, and their strengths and weaknesses in early identification of high-risk MM patients.

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Introduction

Multiple myeloma (MM) is a malignant B-lymphoproliferative disease characterized by infiltration of clonal plasmocytes in the bone marrow, osteolytic lesions of the skeleton, and presence of monoclonal immunoglobulin (M-protein) in serum and/or urine.[1] MM accounts for 10% of all hematologic malignancies.[2] It is the second most common hematologic cancer and represents 1% of all cancer diagnoses and 2% of all cancer deaths.[3] Despite new advances in the treatment of MM, it remains mostly an incurable disease.

MM progresses from a premalignant stage called monoclonal gammopathy of undetermined significance (MGUS).[4] MGUS is a plasma cell proliferative disorder characterized by plasma cell content of less than 10% in the bone marrow, M-protein in serum < 30 g/L, no end organ damage including bone lesions, and no evidence of other B-cell proliferative disorder.[5] Smoldering myeloma (SM), also called asymptomatic myeloma, is an intermediary between MGUS and MM. SM has M-protein in serum ≥ 30 g/L and/or bone marrow plasma cells $\geq 10\%$, and no related organ or tissue impairment or symptoms. Symptomatic MM is a disease characterized by neoplastic proliferation of a single clone of plasma cells producing M-protein, inducing end organ damage, including bone lesions, anemia, renal insufficiency, and hypercalcemia (CRAB symptoms).[5] The comparison of the stages is shown in Table 1.[5]

Extramedullary MM arises outside the bone marrow when the clonal plasma cells are capable of leaving the bone marrow niche and infiltrate virtually any organ. Extramedullary disease can accompany newly diagnosed disease or relapse and has dismal outcome for patients.[6] It is considered a poor prognostic marker in newly diagnosed and in relapsed patients and is more prevalent in genomically defined high-risk MM.

Generally, MM can be divided into 2 subgroups that are approximately equally distributed.[7] Hyperdiploid MM is characterized mostly by numerical gains (eg, multiple trisomies) and few structural changes, and nonhyperdiploid tumors are characterized by many chromosomal rearrangements (eg, translocations involving region 14q32) and sometimes chromosome loss.

MM is a heterogeneous disease at the genetic level and in terms of clinical outcome.[8] The etiology is still unclear and pathogenesis is a complex multifactorial process.[1] It is known that there are some changes in the microenvironment of the bone marrow that allow the tumor to grow while the function of the immune system is decreased. The outcome for patients with MM is highly variable.[9] Although the median overall survival time is 3 to 4 years, the range is from less than 6 months to more than 10 years. Many reports have described a huge number of prognostic factors in MM.[10] In this list, there are many factors that have been confirmed by several studies: the most important parameters are probably $ß_2$-microglobulin, proliferation index, and genetic abnormalities (Table 2).[10]

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Table 1 Stages of MM

MGUS	• M-protein in serum <30 g/L • Bone marrow clonal plasma cells <10% • No related organ or tissue impairment (no end organ damage, including bone lesions) • No evidence of other B-cell proliferative disorders
Asymptomatic (smoldering) myeloma	• M-protein in serum ≥30 g/L and/or • Bone marrow clonal plasma cells ≥10% • No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms
Symptomatic MM	• M-protein in serum and/or urine • Bone marrow clonal plasma cells • Related organ or tissue impairment (end organ damage, including bone lesions)
Extramedullary MM	• No M-protein in serum and/or urine • Extramedullary tumor or clonal plasma cells • Normal bone marrow • Normal skeletal survey • No related organ or tissue impairment (end organ damage, including bone lesions)

Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; M-protein = monoclonal immunoglobulin.
Adapted from International Myeloma Working Group 2003. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003; 121:749-57.

Clinically, relapse is defined as ≥ 25% increase in the serum or urine protein ≥ 0.5 mg/dL; however, the presence of 'biochemical relapse' alone is not an indication for additional systemic therapy. Patients should also have some form of symptomatic relapse before initiation of therapy.[11]

The overall objective of creating a strong staging system for distinguishing patients with different risk is the identification of risk groups that could in particular have improved outcome because they would be considered for different treatment decisions. Novel therapies might benefit patients for whom other therapies fail.[12] In high-risk patients, preliminary reports show high response rates with use of novel drugs, such as bortezomib, lenalidomide, and thalidomide, suggesting that the effect of adverse prognostic factors might be overcome when using this type of therapy. The use of genetic information for risk stratification and treatment selection continues to be investigated in clinical trials and will probably have greater significance for clinical research and patient care in the near future.

Discussion

MM Stratification Systems

First, Durie and Salmon introduced a staging system of 3 different stages, each presented by different levels of selected clinical features that were significantly correlated with measured myeloma cell mass—extent of bone lesions, hemoglobin, and level of serum and/or urine M-protein, serum calcium, and serum creatinine.[13] Creatinine level further defined lower risk (with relatively normal renal function; serum creatinine value < 2.0 mg per 100 mL) and higher risk patients (with abnormal renal function; serum creatinine value ≥ 2.0 mg per 100 mL) in each of the 3 stages. The Durie Salmon system was created predominantly to identify some level of tumor burden at the time of diagnosis, but according to Tuchman and Lonial,[14] its utility in the setting of prognosis in the era of new drugs is a bit limited. However, it is still considered a means of measuring tumor mass and should be mentioned to compare patient's outcome with previously diagnosed cases of MM.[15]

Table 2 Summary of the Most Common Parameters That Accompany Poor Prognosis

Parameter	Poor-Prognosis Values
Plasma Cell Leukemia	
17p Deletion	Present
International Staging System	Stage 3
ß$_2$-Microglobulin	≥5.5 mg/L
Gene Expression Profiling	University of Arkansas 70-gene model or Intergroupe Francophone du Myélome 15-gene model

Adapted from Avet-Loiseau. Ultra high-risk myeloma. Hematology Am Soc Educ Program 2010; 2010:489-93.

In an effort to ensure a more objective classification of patients, the International Myeloma Working Group (IMWG)[9] described the International Staging System (ISS) based on ß$_2$-microglobulin and albumin levels (Table 3).[9] These clinical parameters, chosen because of their wide availability and simplicity of their identification in blood tests, classify MM patients into 3 groups with different overall survival (62 months, 44 months, and 29 months for stages 1, 2, and 3, respectively). ISS has been validated in young and older patients, in patients treated with conventional chemotherapy, autologous stem cell transplantation, or novel agents at diagnosis and relapse, and even though it is more than a decade old, it still represents the most widely used staging system for patients with MM.[16] ISS provides useful information regarding the baseline biological characteristics of the disease. Because of its simplicity and reproducibility, the ISS has demonstrated its value in comparing outcome of clinical trials. However, it has some important limitations, eg, ISS identifies just 3 large prognostic groups, but MM patients are described as a very heterogenic group that cannot be included in only 3 prognostic categories. Identification of the highest risk patients is achieved in only a small number of patients (from 5% to 9%) and better identification of these patients requires a more refined cytogenetic and molecular genetic classification. Another limitation is its focus on prognostication at the population level, so it is not applicable for individualized treatment decisions.[10]

High-Risk Definition Using Cytogenetics

Because only dividing cells can be analyzed, the low proliferative activity of tumor cells early in the disease is a significant limitation of conventional cytogenetics in MM.[8] This limitation has been partly overcome by the use of fluorescence in situ hybridization (FISH), multicolor FISH, comparative genomic hybridization (CGH), and spectral karyotyping. The study of Kapoor et al[17] reinforced the importance of using conventional cytogenetics and interphase FISH (iFISH) for risk assessment. These methods remain independent prognostic tools despite the introduction of novel agents and are now a part of risk stratification models. Most large