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High-risk Multiple Myeloma: Definition and Management

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Abstract

The prognosis of patients with multiple myeloma has significantly improved after the introduction of novel concepts of immunomodulation and proteasome inhibition in myeloma therapies. In conjunction with the use of high-dose therapy and autologous stem cell transplantation, these newer antimyeloma agents facilitated the augmentation of deeper responses and as a result, enhanced survival outcomes. Despite mounting clinical evidence that novel therapies may mitigate the poor prognostic impact of some predictors historically considered "harbingers of doom" in myeloma such as t(4;14), the benefit of these advances is less evident in patients who present with genetically defined high-risk features such as presence of chromosomal abnormalities del17p, t(14;16), or t(14;20), or among patients presenting with plasma cell leukemia. With better understanding of the biology of the disease and further recognition of the genomic instability of the high-risk clonal plasma cell influencing both inherent and acquired therapeutic resistance, newer targeted treatment strategies will hopefully improve prognosis in future among this subset of patients with poorer outcomes. In this review, we not only focus on how to identify the genetically defined high-risk patients with myeloma but also describe the most optimal antimyeloma combination strategies that so far have shown to demonstrate long-term benefits for these patients.

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Introduction

The outcomes among patients with multiple myeloma (MM) have significantly improved with the increased usage of autologous stem cell transplant (ASCT) and other approved combinations of anti-myeloma agents such as immunomodulator agents (IMiDs) thalidomide, lenalidomide, and pomalidomide; proteasome inhibitors (PIs) bortezomib, ixazomib, and carfilzomib; histone deacetylase inhibitors (panobinostat) and the newer generation of antimyeloma therapies, the monoclonal antibodies (elotuzumab, daratumumab). Despite the significant heterogeneity in aggregate, the median overall survival (OS) for patients with myeloma has significantly increased, with some achieving a lifespan similar to their age-matched controls.[1] These advances are a result of understanding of the biology of the disease that led us to minimizing the use of cytotoxic therapies and quickly adapting the use of modern therapies. With newer PIs around the corner (marizomib, oprozomib), molecularly targeted therapies (histone deacetylase inhibitors, HSP90 inhibitors, AKT inhibitors, and KSP inhibitors), and other immunotherapies (monoclonal antibodies such as isatuximab, PD-1 blockade with pembrolizumab) showing promising activity, the reality of achieving a cure for myeloma seems to be within reach. Despite these advances, a subset of patients at the other end of the spectrum, accounting for 15% of patients with myeloma, exhibit a highly aggressive course. These genetically defined high-risk patients exhibit shorter progression-free survival (PFS) after induction or consolidative treatments and are more prone to early and rapid relapses.[2,3] Key concept for bettering the outcomes among these patients is to recognize their genetic risk-stratification earlier in the course of their disease and initiate therapy with a combination strategy of novel agents, followed by ASCT and intense maintenance therapy for a constant suppression of the

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malignant clone.[4] This review is aimed at understanding the appropriate identification of a high-risk patient with myeloma at diagnosis using the commonly available clinical and genetic data and summarizing the data on the antimyeloma activity of the currently available agents among high-risk patients with myeloma.

Diagnostic Determinants for Risk Stratification

International Staging System (ISS)

In myeloma, the most widely accepted prognostic system is the ISS, which stratifies patients into 3 groups based on the routinely used lab values of serum albumin and β2-microglobulin (β2m).[5] The ISS was developed from clinical and lab data using 10,750 newly diagnosed patients with symptomatic myeloma across 17 institutions. Using β2m and albumin, patients were stratified into stages I, II, and III, conferring a median overall survival (OS) of 62, 44, and 29 months, respectively. Compared with the Durie-Salmon staging system, the ISS is more reproducible and easier to compute and reflected both patient and tumor factors: β2m being a measure of tumor bulk and renal function, whereas albumin reflected the patient's general state. For the most part, the ISS has now replaced the Durie-Salmon staging system, as it does represent a better way to assess outcomes. The major limitation of this model is the fact that it does not incorporate genomic or proliferation-related aspects.

Fluorescence In Situ Hybridization (FISH) and Cytogenetics

As in other hematologic malignancies, cytogenetic abnormalities comprise one of the most important prognostic factors for myeloma. Among the newly diagnosed patients with myeloma, along with morphologic diagnosis on the analysis of bone marrow plasma cells, metaphase cytogenetics and interphase FISH studies using specific panel of probes should be investigated. Given the low yield of plasma cells in the bone marrow aspirate, and the lower proliferative index of plasma cells, metaphase cytogenetics may fail to provide reliable information for risk stratification. FISH may be a very high-yield alternative for evaluating these chromosomal abnormalities in the bone marrow samples, purified for CD138-expressing plasma cells. FISH testing can reveal abnormalities in $>$ 90% of patients but only provides information on regions interrogated by probes. The panel at a minimum should include probes for the detection of the most frequent chromosomal aberrations in myeloma: gain (1q21), del(1p), del (13q14), 14q32, and translocations t(4;14)(p16;q32), t(11;14) (q13;q32), t(14;16) (q32;q23) and t(14;20)(q32;q11), and del (17p13); trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21.[6]

Gene Expression Profiling (GEP)

Routine use of metaphase cytogenetics and FISH has allowed a better understanding of the spectrum of genetic aberrations and identification of abnormalities associated with poor outcomes.[6,7] However, these abnormalities alone do not account for the heterogeneity and have led to the evaluation of other approaches. GEP is a powerful technique to identify the expression of several prognostic genes and pathways and provides insights into other biological processes such as cell proliferation.[8,9] Using the GEP signatures, it is potentially possible to accurately classify patients into high-risk and low-risk GEP phenotypes.

The University of Arkansas for Medical Sciences (UAMS) group was the first to identify a 70-gene panel, and subsequently refined a 17-gene signature that is prognostic for survival. The 13% of the patients identified as high-risk had unfavorable event-free survival (EFS) and OS.[10] Interestingly, 30% of the original 70 genes in this GEP signature were located on chromosome 1, and increased copy numbers of CKS1B and the IL-6 receptor mapping within a minimally amplified region of chromosome 1q21 were found to be correlated with poor outcome in MM.[10] Based on a transcriptome study using GEP, the UAMS group detected 7 subtypes of MM: PR (proliferation), LB (low bone disease), MS (MMSET), HY (hyperdiploid), CD-1 (CCND1), CD-2 (CCND3) and MF (MAF/MAFB). HY, CD1, CD2, and LB comprised the low-risk group, with 3-year actuarial survival probability of 81% to 88% with Total Therapy (TT) 2, whereas the 2 high-risk groups, MS and PR, had inferior overall survival (69% and 55%, respectively) and did not appear to benefit from this therapeutic strategy.[11] Barlogie et at demonstrated that TT3 incorporating bortezomib, in comparison with its predecessor protocol TT2, markedly improved clinical outcomes of approximately 85% of patients presenting with GEP-defined low-risk myeloma.[12] In further analyses of TT3 and its successor trial 2006-66, the patients with a high-risk GEP70 signature still continued to have a poor outcome.

Several GEP signatures have been proposed by different groups. Decaux et al from the International Myeloma Foundation (IFM) group identified a set of 15 genes that defined 25% of the patients as high-risk.[13] Other GEP signatures such as the one developed by the Medical Research Council (MRC) Myeloma IX trial using 6 genes, also appear to have high prognostic value.[14] It is interesting to note that, although both these studies have included patients undergoing high-dose therapy, the UAMS 17-gene signature, IFM 15-gene signature, and MRC 6-gene signature do not share common genes.[10,13,14] The lack of overlap in the genes constituting the different GEP signatures relates to the different ways in which these signatures are generated. Given the complexity involved in routine interpretation of GEP results, platforms such as MyPRS (microarray-based GEP) that utilize the statistical and bioinformatic algorithms potentially can generate a GEP report that is easily interpretable and understandable and can help with decision-making in a routine clinical setting.[15]

There are limited prospective head-to-head prognostic comparisons existing for these GEP signatures, making it difficult to rely on any one defined prognostic signature. Among the newly diagnosed patients with myeloma receiving lenalidomide and dexamethasone (Rd), Kumar et al examined the utility of 2 GEP-based risk stratification systems, GEP70[10] and GEP15,[13] and identified a high-risk group with a dismal outcome compared with the remaining patients (with GEP70 risk score time-to-progression [TTP], 9 months vs. 23 months; $P = .3$; with GEP15 risk score TTP, 16 months vs. 23 months; $P = .3$).[16] Lastly, analyses of data resulting from the intersection of high-risk patients between a new prognostic signature of 92 genes obtained from newly diagnosed patients with MM included in the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) 65/GMMG-HD4 trial and previously