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High-Risk Multiple Myeloma in 2026: Evolving Definitions and Therapeutic Options

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Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by osteolytic bone disease, anemia, kidney disease, and hypercalcemia, resulting in significant morbidity compared to age-matched controls.[1] Treatment has advanced considerably over the past 20 years; the current standard of care involves treatment with quadruplet regimens combining a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and dexamethasone, with a CD38 monoclonal antibody.[2] Eligible and fit patients will proceed with autologous stem cell transplantation (ASCT), and, following initial therapy, all patients receive maintenance therapy, typically lenalidomide and a CD38 monoclonal antibody.[2] For elderly or frail patients, regimens such as daratumumab plus lenalidomide, or lenalidomide plus bortezomib, with or without dexamethasone, may be considered, but most patients will tolerate four drug regimens well.[3] These treatment combinations have resulted in dramatic improvements in both progression-free survival (PFS) and overall survival (OS); the phase III PERSEUS trial reported a 2-year PFS of 84.3%.[4] Even with the use of older triplet regimens and ASCT, real-world data document a median OS of ~10 years.[5,6]

However, not all patients will achieve these outcomes. A subset of patients with MM has poorer outcomes even with state-of-the-art treatment with quadruplet regimens, which is broadly defined as high-risk multiple myeloma (HRMM).[7] Patients with HRMM have earlier relapses, more aggressive disease biology, and shorter remissions with standard-of-care treatments. They can also be more prone to the development of aggressive presentations, such as extramedullary plasmacytomas (EMP), anaplastic morphology, and secondary plasma cell leukemia. The hallmark of all these subtypes is treatment refractoriness—defined as a lack of durable responses to standard effective treatments.

Herein, we review the definition of HRMM, outcomes with standard treatment, and preferred treatment approaches for a patient with *de novo* or functional HRMM in the Canadian treatment landscape.

Risk Factors

HRMM can be broadly thought of in two ways: one, through well-defined "classical" chromosomal changes or pathologic findings that increase risk of aggressive disease and early relapse; or, *dynamic* risk assessment (sometimes called functional HRMM) based on the early onset of progressive disease, often among patients without traditional high-risk markers.[8,9] It is likely that, with improved genomic risk assessments, many patients who were considered standard-risk MM may be better classified as HRMM, thereby improving the *a priori* risk assessment of newly diagnosed MM.[10,11]

In this review, we explore these concepts and develop a unified definition of HRMM before addressing the treatment approach to high-risk disease.

Current High-Risk Definitions

Chromosomal Factors

The most frequently used tool for MM risk assessment is chromosomal analysis by fluorescent in situ hybridization (FISH). The chromosomal changes considered to be high risk

Chromosomal Abnormalities	Details
Loss of *TP53*: chromosome 17	**Deletion 17p:** Deletion of the long arm of chromosome 17, resulting in loss of *TP53*[34] *TP53* mutations: mutations causing deactivation of the *TP53* gene[34] ***Must be present in ≥20% of nucleated cells to be significant, as per recent IMWG/IMS guidelines[8]
***IGH* translocations: chromosome 14, immunoglobulin heavy-chain locus at 14q32**	**t(4;14):** *FGFR3-IGH* translocation – deregulation of fibroblast growth factor[35] **t(14;16):** *MAF-IGH* translocation - deregulation of *c-MAF* proto-oncogene[36] **t(14;20):** *MAFB-IGH* translocation – deregulation of *MAFB* oncogene[37] **t(8;14):** *MYC-MAF* translocation – uncommon, results in rearrangement of MYC oncogene[38]
Chromosome 1 abnormalities	**1q+:** Gain (2 copies) vs. amplification (>3 copies); CKS1B – activation of cyclin dependent kinase, deregulation of cell cycle control[39] **Del(1p):** Several genes implicated; however, the underlying driver remains unknown[39]
Complex karyotype	≥3 chromosomal abnormalities on a conventional karyotype with G banding; associated with worse prognosis in many series[40]
Biologic Features	
Beta-2 microglobulin	Serum marker of tumor burden in newly diagnosed MM, with elevated values portending worse prognosis; may be affected by underlying kidney function[8] *New IMWG/IMS guidelines restrict this to patients with normal creatinine (<1.2 mg/dl or <106 µmol/L).
Lactate dehydrogenase (LDH)	Marker of cell turnover; elevated values above the upper limit of normal associated with more rapidly proliferative disease. Incorporated into the Revised ISS staging system[15]
Circulating tumour cells	Plasma cell leukemia – extreme example of this, defined as >5% circulating plasma cells on manual differential[17] The presence of any circulating plasma cells at the time of diagnosis, and prior to ASCT, has been shown to be a negative prognostic indicator in retrospective series[41]
Anaplastic morphology	Uncommon presentation, more commonly seen in relapsed multiple myeloma, treatment resistant and poor prognosis. Characterized by pathologic finding of poorly differentiated, pleomorphic, and significantly enlarged plasma cell[16]
Extramedullary disease	Generally defined as plasmacytomas arising outside the bone marrow, without direct connection to the bones. When presenting in a patient with newly diagnosed or relapsed disease, portends poor outcomes[42]

Table 1. High-Risk Features in Newly Diagnosed Multiple Myeloma; *courtesy of Andrew J. Cowan, MD, Kevin Song, MD, Florian Kuchenbauer, MD, and Christopher P. Venner, MD.*

Abbreviations: ASCT: autologous stem cell transplant; **HRMM:** high-risk multiple myeloma; **IMWG/IMS:** International Myeloma Working Group and International Myeloma Society

Criteria for HRMM[8]
Del(17p)* and/or *TP53* mutation**
IGH translocations: t(4;14), t(14;16), or t(14;20), co-occurring with 1q+ and/or del(1p32)
Monoallelic del(1p32) with 1q+, or biallelic del(1p32)
High beta-2 microglobulin (>5.5 mg/dL) with normal creatinine (<106 µmol/L)

Table 2. IMWG/IMS Consensus Genomic Criteria for High-Risk Multiple Myeloma; *adapted from Avet-Louiseau et al., JCO 2025.*[8]

*Cancer clonal fraction ≥20% by analyses of CD138-positive cells
**Assessed by a next-generation sequencing-based method

Abbreviations: HRMM: high-risk multiple myeloma; **1q+:** gain (3 copies) or amplification (>=4 copies) of the long arm of chromosome 1

in MM include chromosome 14 immunoglobulin heavy chain locus (*IGH*) translocations, including t(14;16), t(4;14), t(14;20); the deletion 17p resulting in loss of *TP53*; and chromosome 1 changes, such as the 1q gain or 1p deletion (**Table 1**).[8] Additionally, TP53 mutations have been associated with worse outcomes.[12] These risk factors form part of the recently published guidelines for determining high-risk disease.[8] Although many of these were originally defined in the context of doublet or triplet upfront treatment combinations, recent data continue to show the negative impact of these high-risk chromosomal changes, albeit with some nuance, and dramatically improved outcomes with quadruplet-based regimens.[13] Based on recent analyses of patients treated with quadruplet regimens in newly diagnosed MM, the presence of two or more high-risk cytogenetic features appears to confer the highest risk for early disease progression.[14]

Biologic Risk Factors

Several other surrogate markers can help understand which patients are more prone to aggressive disease biology (**Table 1**). Beta-2 microglobulin, included in the Revised International Staging System (R-ISS) for M15, is a surrogate marker of MM tumour volume. Further, anaplastic morphology, which can occur *de novo* but is more frequently described among patients with heavily treated MM, confers treatment resistance and poor outcomes.[16]

Plasma cell leukemia (PCL) is a high-risk subtype of MM, defined by the presence of >5% circulating plasma cells on the peripheral smear differential.[17] Although considered a separate diagnosis, it is just the leukemic phase of MM, representing a more advanced form of the disease. It may be present at diagnosis (primary PCL) or with relapse (secondary PCL). Patients with PCL have much poorer outcomes in general, even with the advent of modern therapies. The translocation t(11;14) is present in approximately half of patients with primary PCL and appears to be associated with improved prognosis.[18] Despite PCL being on the MM spectrum of disease, reflecting the most aggressive clinical phenotype, it is often excluded from trials, thereby limiting data that could contribute to optimizing treatment approaches.

Expert Driven High-Risk Criteria: The 2025 IMW/IMS High-Risk Classification

Recently, the International Myeloma Working Group and International Myeloma Society (IMW/IMS) published the results of a working group recommendation for the definition of HRMM. Considering the significant progress in treating newly diagnosed MM, the group aimed to improve on the previous International Staging System (ISS) and the revised ISS (R-ISS), which were developed using older datasets and treatments that are less relevant now. In summary, the group determined a new set of criteria, the Consensus Genomic Staging (CGS) of HRMM (**Table 2**).[8] These new criteria build on the R-ISS but also emphasize the importance of co-occurring chromosome 1 abnormalities and the significance of beta-2 microglobulin in patients with normal kidney function.

Primary Refractory/Functional HRMM

A different way to examine HRMM is not as an *a priori* determination, but rather as a dynamic assessment of risk over time. Several analyses have confirmed that patients who experience early relapse (often called functional HRMM [FHRMM]) have much more aggressive, treatment-resistant disease and poorer survival compared to other patients.[19-21] In the MRC XI trial, patients who experienced relapse within 12 months of ASCT had a 3-year OS of 28% compared to 53% amongst those who did not, with similar results reported in a French analysis.[22,23] In a subanalysis of the adaptive trial MASTER, which utilized daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) as front-line treatment, patients who relapsed within 36 months were a subset who fared poorly even with the successful use of salvage regimens.[24] Thus, patients who experience early relapse after successful front-line induction with triplets (<24 months) or quadruplet regimens (<36 months), should also be considered as having FHRMM irrespective of initial chromosomal abnormalities. Indeed, up to 44% of patients in the MASTER cohort who relapsed within 36 months did not have high-risk chromosomal changes at the time of diagnosis.

Identification of HRMM: Future Directions

Although we have refined our classification of HRMM using the recent IMWG/IMS CSG criteria, as evidenced by the emerging recognition of FHRMM, not all patients are accurately identified as having HRMM at the time of diagnosis. Better tools are needed to accurately identify these patients. Gene expression profiling (GEP) has been used to more accurately risk-stratify patients at diagnosis and has shown some success in categorizing patients better than traditional chromosomal analysis.[10,25] Two such tools are available: the GEP70/UAMS70 and the EMC92 assays; however, neither is broadly available in Canada, nor is it currently funded through public means.[25] For example, in one analysis of 94 patients using the GEP70/UAMS70 assay, relapse rates were 28% among patients with a high-risk GEP70 result but only 2% among those classified as low risk.[26] Additionally, early relapse was documented in 30% of patients with high-risk GEP70 scores and low-risk chromosomal abnormalities, but there were no patients with low-risk GEP70 scores and high-risk chromosomal changes who had early relapse.

Recent analyses have also implicated genomic signatures from the apolipoprotein B mRNA-editing catalytic polypeptide-like (APOBEC) family of deaminases as potentially driving MM progression, which may also help better classify HRMM at diagnosis. In a recent publication, APOBEC classifiers were shown to help improve MM risk assessment.[27] In another recent analysis of newly diagnosed MM in the CoMMpass study, high APOBEC mRNA expression was associated with hyper-APOBEC mutations and was more common in MM cells with genomic instability and increased replication stress.[28]

Taken together, gene expression profiling and a better understanding of the importance of APOBEC expression patterns may be promising modalities for improved risk assessment. At present, GEP panels are limited globally, so further efforts are needed to expand access across all MM treatment centres.

Therapeutic Options

One of the major challenges in treating HRMM has been the lack of high-quality, randomized, prospective trials in this patient population. As such, guidance for the management of HRMM has often been based on expert opinion, sometimes informed by retrospective analyses and datasets. In general, however, the treatment of newly diagnosed HRMM, as defined above, would involve applying the standard treatment algorithms for newly diagnosed MM in Canada. Presently, this would be with a quadruplet regimen containing an anti-CD38 monoclonal antibody, IMiD, PI, and dexamethasone, with ASCT in eligible patients, followed by consolidation quadruplet therapy, after which the patient will receive anti-CD38 antibody and lenalidomide maintenance. For years, older trials, such as the HOVON-65 trial, demonstrated the apparent superiority of bortezomib in patients with certain high-risk chromosomal abnormalities, leading some expert recommendations to advise the use of PIs for maintenance in HRMM.[29] However, the data that support these recommendations are not consistent with modern treatment paradigms. These studies had control arms ranging from observation, steroids, or thalidomide treatment. There is no prospective comparison of bortezomib and lenalidomide, and more contemporary approaches suggest that multi-agent maintenance is the most beneficial for these patients. This could be achieved with prolonged PI-IMiD combinations

(challenging given long-term neuropathy risk, time toxicity, and general tolerability) or, more recently, with an anti-CD38 antibody and lenalidomide. The latter are now recommended based on large, randomized trials, such as PERSEUS, CEPHEUS, GMMG-HD7, and IMROZ.[4,30-32]

For patients who experience early relapse, the next line of therapy must consider the refractoriness status to previously used therapies. Looking ahead, these patients have usually been exposed to and are almost universally resistant to both anti-CD38 antibodies and lenalidomide. In a recent analysis of patients with FHRMM from the MASTER trial (all of whom received front-line quadruplet therapy), the best results appeared to be achieved with T cell-engaging therapies (TCE), such as bispecific antibodies or chimeric antigen receptor (CAR) T-cell therapy.[24] Presently, many jurisdictions await funding of CAR T-cell therapy for early relapse. Even when available, these high-risk patients face a challenging path to treatment given the potential of high tumour burden and rapidly progressing disease prior to CAR T-cell infusion. While bispecific antibodies are more accessible, access is often restricted to patients who have reached the 4th treatment line or beyond. Ideally, if access were not an issue, these patients should be sequenced early in relapse. Both retrospective (*post-hoc* analysis of MASTER) and prospective (MajesTEC3) data highlight the impressive depth of responses and encouraging PFS regardless of cytogenic risk.[33] More data are needed on the durability of the response in FHRMM. However, it is important to reiterate that outcomes with more traditional regimens in either a primary refractory or early relapse setting after lenalidomide + anti-CD38 are abysmal.

Summary

Although definitions have evolved over the years, specific chromosomal abnormalities and combinations, as well as elevated beta-2 microglobulin, remain the cornerstone of defining HRMM. Patients with MM who meet the new CSG criteria for high-risk disease, or those who have early relapse (FHRMM), fare poorly compared to other patients. Although benefits from modern MM treatment with quadruplet regimens, ASCT, and dual CD38/IMiD maintenance are observed, a proportion of patients have less durable remissions or outright refractoriness. These patients require novel approaches after establishing triple-class-exposed/refractory status. Early use of TCE therapies should be considered and advocated for. Overall, better tools are necessary to *a priori* define these high-risk patient populations with definitions tailored to the specific therapeutic context.

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