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High-risk myeloma: Definitions and treatments

Rintu Sharma, MD
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Introduction

Multiple myeloma is characterized by clonal proliferation of biologically heterogeneous plasma cells, leading to diverse clinical presentations and outcomes. Although outcomes have improved dramatically over the past decade with the rapid change in the treatment paradigm in standard-risk myeloma, a subset of patients remains who respond poorly to treatment and experience early relapses.[1,2] These patients are considered high-risk and can be identified at the time of diagnosis based on several factors and their response to treatment **(Table 1)**. Therefore, it is important to consider high-risk status as a dynamic assessment.

High-risk myeloma - definition

A) At diagnosis:

1. Disease and patient-related factors:
i) Cytogenetics and staging: Traditionally, patients were defined as high-risk based on advanced international staging system (ISS) stage and later, the revised ISS (R-ISS), which incorporates the presence of elevated lactate dehydrogenase (LDH) and/or certain cytogenetic fluorescence *in situ* hybridization (FISH) abnormalities, including t(4;14), t(14;16), and deletion of 17p, to better demarcate the survival outcomes in this group. The estimated 5-year overall survival (OS) of R-ISS I is 82%, compared to 40% for R-ISS III.[3,4] Although other abnormalities like t(14;20) and monosomy 13 have also been identified as high-risk, these were not included in R-ISS because of their lower prevalence.[5] With the identification of copy number alterations in chromosome 1q as a poor prognostic marker, R-ISS 2 and mSMART classifications incorporate 1q gain/amplification in the staging, allowing a better stratification of patients into four groups.[6,7] Deletion of 1p is another adverse feature but is yet to be incorporated into the current R2 ISS system.[8] Patients with the co-existence of more than one high-risk chromosomal abnormality are categorised as ultra-high risk and have even worse survival outcomes compared to their counterparts with no or one high-risk cytogenetic abnormalities.[9,10]

ii) Gene expression profiling assays like SKY92 and GEP 70 utilise the expression of messenger RNA to identify mutational signatures that are independent prognostic markers to predict early relapses.[11,12] Several genes involved in DNA damage repair pathways, glycolysis, oxidative stress, epithelial-mesenchymal transition, and numerous factors in the tumour microenvironment have been recognised as risk factors for early relapse; however, a detailed discussion of these is beyond the scope of this review.[13]

iii) Patients presenting with renal failure have worse outcomes compared to patients who present with normal renal function, even if the kidney function is recovered.[14] Additionally, extramedullary plasmacytomas, central nervous system involvement, and primary plasma cell leukemia (PCL) also represent aggressive disease biology, respond poorly to treatment, and have a shorter progression-free survival (PFS) and OS, and as such are a high-risk population requiring aggressive treatment.[15,16]

iv) Patient-related factors: the international myeloma working group (IMWG) identified a significant impact of geriatric assessment on the survival and toxicity prediction in elderly patients with myeloma enrolled in several clinical trials with frail patients having a shorter OS (57% at 3 years) than fit patients (84% at 3 years), which may guide myeloma physicians for better decision-making.[17]

B) Based on the response to treatment:

Functional high-risk (FHR): Patients who are not labelled as high-risk at diagnosis but progress within 12-18 months of therapy or are refractory to treatment despite an optimal initial therapy are considered functional high-risk and have significantly inferior PFS and OS.[18,19] These patients can only be assessed by dynamic response assessments. Failure to achieve very good partial response (VGPR) or better has been reported as an independent factor predicting an early relapse within 12 months of high-dose chemotherapy treatment, translating to a significantly worse OS.[20,21] A common observation in these studies was the mislabelling of almost a quarter to half of the functional high-risk patients as standard risk because they fell into the ISS-I or II subgroups with standard-risk cytogenetics. Several scoring systems have been devised to identify early relapses and functional high-risk, which incorporate different combinations of age, performance status, markers of high tumour burden (high LDH, albumin, bone marrow plasma cells), ISS stage, and disease status at autologous stem cell transplantation (ASCT), which could be integrated into daily clinical practice.[22-24]

Sustained minimal residual disease (MRD) negativity is a better prognostic marker than VGPR; however, its routine use in clinical practice is yet to be established.[25]

Thus, defining high-risk patients requires a comprehensive baseline assessment with longitudinal response monitoring and, thus, is a dynamic process and should not be limited to baseline R-ISS and cytogenetic abnormalities.

At Diagnosis:	
Disease-related factors o High tumour burden/ aggressive clinical presentation	High LDH, extramedullary disease, central nervous system involvement, primary plasma cell leukemia, renal failure
o Cytogenetic abnormalities	Primary cytogenetic abnormalities: t(4;14), t(14,16), t(14;20); secondary cytogenetic abnormalities: 17p deletion, 1q gain/ amplification, 1p deletion
o Staging systems: R-ISS, R2- ISS	**R- ISS III**: beta 2 microglobulin >5.5 mg/L with either raised serum LDH and/or positive del 17p, t(4;14), or t(14;16) by FISH. **R2- ISS**: Scoring system incorporating ISS II or III, del17p, high LDH, t(4;14), or presence of 1q gain/amplification with an additive score of 3-5 **mSMART** classification: high-risk abnormalities include t(4;14), t(14;16), t(14;20), del 17p, or p53 mutation, chromosome 1q abnormalities (1q gain or 1p deletion), gene expression profiling high-risk signature.[7] Sky 92, UAMS/ GEP 70
o Gene Expression Profiling	IMWG frailty score R-MCI
Patient-related factors o Frailty	
After treatment	
Functional high-risk	• Primary refractory patients • Patients who progress within 12-18 months of initiating optimal therapy.

Table 1. Definition of High-Risk Myeloma. *Courtesy of Guido Lancman, MD, MSc, Rintu Sharma, MD and Karla Alexandra Sánchez Hernández, MD*

Abbreviations: FISH: fluorescence in situ hybridization; **IMWG:** international myeloma working group; **LDH:** lactate dehydrogenase; **mSMART:** Mayo stratification for myeloma and risk-adapted therapy; **R-ISS:** revised international staging system; **R-MCI:** revised myeloma comorbidity index

What are we doing today to treat high-risk multiple myeloma?

In Canada, the current standard of care (SOC) treatment for newly diagnosed patients with multiple myeloma (MM) who are eligible for transplant, regardless of the presence of high-risk features at diagnosis, is the VRd regimen (bortezomib, lenalidomide, and dexamethasone). The DETERMINATION trial showed that VRd induction, followed by ASCT, VRd consolidation, and lenalidomide maintenance, resulted in a median PFS of 67.5 months. However, in the subgroup of patients with at least one high-risk cytogenetic abnormality (HRCA), the PFS dropped to 55.5 months and 35.9 months for patients with ISS III at diagnosis, respectively.[26] In other countries, quadruplet therapies are now being used as the first line of treatment for newly diagnosed MM, with the addition of anti-CD38 monoclonal antibodies to the VRd therapy. The Phase 3 PERSEUS trial added subcutaneous daratumumab to the VRd regimen (D-VRd) during induction, consolidation, and maintenance in transplant-eligible patients. After a median follow-up of 47.5 months, the PFS was significantly improved with D-VRd to 84.3% compared to 67.7% for VRd.[27]

Although the quadruplet treatment showed consistent benefits for the high-risk population compared to the VRd arm, the outcome comparison between patients with ISS III or HRCA versus ISS I-II or standard risk cytogenetics (SRCG) within the D-VRd group did show slightly inferior results. The patients with ISS III achieved a complete remission (CR) or better rate of 80%, while the group with ISS I and II had a rate of 89.8% and 88.6%, respectively. Similarly, patients with HRCA had a CR or better rate of 82.9%, while patients with SRCG had a rate of 88.6%. Further follow-up will be needed to determine the PFS achieved with this regimen in these patient groups.[28] At this time, the addition of daratumumab to VRd is recommended for high-risk Canadian patients who can access it through private insurance, as it is not yet publicly funded.

High-dose melphalan and ASCT improve outcomes in patients with MM; therefore, ASCT remains a SOC treatment in all patients with a performance status suitable to undergo the procedure. Patients who receive VRd alone have a 53% higher risk of experiencing events like disease progression or death, compared to those who undergo an ASCT after VRd induction.[26]

In contrast, the effectiveness of tandem transplants is not yet fully established. According to the EMN02/HO95 study, in comparison to single ASCT, tandem transplants showed better results in terms of prolonged PFS and OS for both the general patient population and poor prognosis subgroups.[28] The STaMINA trial showed no difference between single and tandem transplants in the overall population, but there appeared to be significantly longer PFS for high-risk patients receiving tandem vs. single transplants.[29]

Tandem transplant remains a suitable option for treating high-risk patients, although it is not universally adopted. Our center (Princess Margaret Cancer Centre, Toronto, ON) conducted a retrospective review, which revealed that patients with high-risk disease who underwent tandem transplantation had a significant improvement in both PFS and OS compared to those who received single ASCT.[30] The median PFS for patients who underwent tandem transplantation was 45 months, and the median OS was 68.5 months. In contrast, patients who received a single ASCT had a median PFS of 24.9 months and a median OS of 29.3 months. It should be noted that this analysis was conducted before the establishment of VRd or D-VRd as induction regimens, and, therefore, it cannot fully evaluate the results of tandem transplants in combination with VRd or quadruplet regimens.

Maintenance treatment plays a crucial role in the treatment of patients with MM, especially in high-risk patients who can achieve deep, but not durable, responses. The Total Therapy 3 (TT3) clinical trial conducted in 2007 was a pioneer in incorporating a proteasome inhibitor (PI), bortezomib, along with the immunomodulatory drug (IMiD) thalidomide as maintenance. When compared to the results of the Total Therapy 2 trial (TT2), patients under 65 years of age and those with gene expression profiling (GEP)-defined high-risk MM showed a significant improvement in the 2-year event-free survival (EFS) and OS with the addition of bortezomib. The TT3 group had a 2-year EFS of 68% and OS of 75%, while the TT2 group had a 2-year EFS of 30% and OS of 50%.[31] The use of dual maintenance (PI/IMiD) is now a SOC practice in treating high-risk MM. A randomized phase 3 trial demonstrated no benefit of adding ixazomib to lenalidomide for maintenance, including in the subgroup of high-risk patients.[32]

Several clinical trials in patients with newly diagnosed MM have incorporated anti-CD38

monoclonal antibodies to lenalidomide during maintenance treatment. However, these studies were not specifically designed to evaluate its efficacy during maintenance and although it is a viable alternative, more information is required before it can be incorporated into day-to-day clinical practice.

What is being investigated for patients with high-risk MM?

The treatment for myeloma is constantly developing, leading to improved patient outcomes across all subgroups. Unfortunately, there remains a discrepancy between patients with high-risk and standard-risk disease. As such, various initiatives aim to overcome these differences.

Carfilzomib and bortezomib are both PIs. Despite their similarities, there are subtle differences in their mechanisms of action. Carfilzomib is an irreversible inhibitor of the 26S proteasome complex, while bortezomib is a reversible inhibitor. Notably, a head-to-head comparison of these drugs demonstrated a significant improvement in OS with carfilzomib over bortezomib in patients with relapsed or refractory MM (RRMM).[33]

This principle has resulted in the inclusion of carfilzomib as a first-line treatment for high-risk patients with newly diagnosed MM. The effectiveness of D-KRd (carfilzomib, lenalidomide, dexamethasone, and daratumumab) for induction/consolidation therapy has been studied in various Phase 2 clinical trials, such as the MASTER and IFM 2018-04 studies, which have demonstrated improved outcomes and feasibility among this patient population.[34,35] Further research is needed to determine its use outside the clinical trial setting.

First-line quintuplet treatments have also been studied as an alternative approach for patients with ultra-high-risk MM. The treatment protocol in the OPTIMUM Phase 2 trial included D-CVRd (cyclophosphamide, bortezomib, lenalidomide, dexamethasone, daratumumab) induction, V-augmented ASCT, extended D-VRd consolidation, and daratumumab-lenalidomide (D-R) maintenance. This trial used the ultra-high-risk patients from the Myeloma XI trial as the external comparator arm. The results showed significant improvement in PFS and OS, with a PFS of 77% compared to 39%, and an OS of 83.5% compared to 73.5% at a 30-month follow-up, for patients treated with this regimen vs. the patients from the Myeloma XI trial, respectively.[36]

Immunotherapies, such as anti-B cell maturation antigen (BCMA) chimeric antigen receptor CAR T-cells and bispecific antibodies, have shown impressive efficacy in heavily pretreated patients with RRMM; however, high-risk subgroups remain a challenge. In the 2-year follow-up of the phase 1b/2 CARTITUDE-1 study of cilta-cel (anti-BCMA CAR T), PFS was shorter in patients with ISS 3, high-risk cytogenetics, plasmacytomas, and high tumour burden as compared to the overall study population.[37] Lower efficacy has also been observed in these subgroups for bispecific antibodies.[38,39] It remains to be seen whether using these therapies earlier in the disease course can abrogate some high-risk features. In the phase 3 CARTITUDE-4 trial, cilta-cel appeared superior to SOC for all high-risk subgroups, but further data are needed to understand the durability of this response compared to standard-risk patients.[40]

Final Recommendations:

- High-risk disease is a dynamic concept. Identifying high-risk features at diagnosis and throughout the course of the disease is crucial for appropriate management.
- Tumor burden, cytogenetic abnormalities, ISS staging, gene expression profile, suboptimal response to treatment, and frailty are all components of high-risk disease.
- Quadruplet induction regimens are preferred over triplet regimens where accessible.
- ASCT remains crucial in the treatment of patients with MM; tandem transplantation can potentially offer improved outcomes when compared to single ASCT.
- Novel approaches to maintenance are being explored, including anti-CD38 antibodies and immunotherapeutic (CAR T-cell and bispecific T cell engager [BiTE]) approaches.
- New immunotherapies, such as anti-BMCA CAR T-cell and BiTEs, have shown positive results in treating patients with high-risk MM. They are currently only used for relapsed/refractory cases. Incorporating these therapies in the first-line setting may help overcome the poor prognosis in this group of patients.

Conclusions

When treating patients with newly diagnosed MM, early detection of high-risk features is crucial to provide treatments that can result in deep and long-lasting remissions. A uniform way of defining

patients with high-risk MM is yet to be developed as there is significant heterogeneity within this group. It is evident that correctly identifying this population requires an evaluation of more factors than just cytogenetics, and high-risk disease is a dynamic entity rather than a single determination performed only at diagnosis.

When selecting a treatment, it is important to not only consider effectiveness but also the potential side effects of the chosen regimen. Additionally, the patient's characteristics and preferences, disease biology, comorbidities, and available treatments and supportive treatments should be considered carefully. These factors are crucial in determining the most appropriate regimen for each scenario. Where available, high-risk patients should be referred for clinical trials.

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Financial Disclosures :

G.L.: None declared.
R.S.: None declared.
K.A.S.H.: None declared.

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