High-risk Myeloma – Section 9

Management of High-Risk Multiple Myeloma Patients

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Take-home messages:
- Treatment of high-risk (HR) patients should be flexible, and adapted to eradicate all malignant cells (minimal residual disease).
- Available new drugs improve the outcome of patients with HR cytogenetic abnormalities but have not so far been able to overcome adverse prognoses.
- Innovative therapies, such as CAR-T cells or T-cell engager antibodies, should be explored early in the course of the disease.

Introduction

Survival of multiple myeloma (MM) has significantly improved in the last decade. However, this improvement has not been uniform, with some patients achieving long-term remission and being potentially cured, whereas others have a dismal prognosis. Identification of this second high-risk (HR) patient population is crucial to guiding patient information and treatment. We usually consider HR patients to be those with adverse cytogenetics and high tumor burden (ISS, β2-microglobulin, LDH), which have been classified as R-ISS3. However, other parameters also account for HR, such as extramedullary disease or a high frequency of circulating plasma cells (PCs), together with frailty or co-morbidities. All this information can be obtained at baseline. However, risk is dynamic, and response and resistance to initial treatment are known to be of utmost importance. In this setting, early relapses and primary refractory disease should be considered an ultra-HR category. Current data show that the best way to overcome HR disease is to achieve and particularly to sustain minimal residual disease (MRD) negativity inside and outside the bone marrow (BM). Accordingly, treatment selection in this HR population should be adapted to achieve this goal and therefore our recommendation is to use as induction therapy those drug-combinations that ensure the higher rate of MRD.

Management of HR disease

In newly diagnosed transplant-eligible patients with HR MM, our recommendation is to use as induction therapy those drug-combinations that ensure the higher rate of MRD. This should include 4 to 6 cycles of a 3- or 4-drug combination with a proteasome inhibitor (PI) (Bortezomib or Carfilzomib) + immunomodulatory drug (IMiD) (Lenalidomide or Thalidomide) + Dexamethasone or if possible, an anti-CD38 monoclonal antibody (Daratumumab or Isatuximab, when approved). With these schemas post-induction complete remission and MRD-negative rates ranging from 16% to 33% have been reported for Daratumumab-VTD, VRD-GEM or KRD. The former has been already approved as a new standard of care and is waiting for reimbursement in several countries in Europe. Moreover, in the Cassiopeia trial, obtaining MRD after induction with Daratumumab-VTD was associated with significant PFS advantage (personal communication). It should be noted that different schemas with the same drugs can yield different results, which may reflect the importance of dose density in this setting. Moreover, comparisons across trials are difficult, particularly if done with respect to CR (the implementation of defining criteria are quite variable), and for this reason it is probably better to focus on MRD and PFS (Table 1).

Intensification with high-dose melphalan and autologous stem cell transplant (ASCT) remains a standard of care for young MM patients and especially in HR disease. Indeed, even in the context of very good induction, ASCT can induce a higher percentage of persistent MRD negativity after 1 year in HR patients (R-ISS 2 & 3) compared with 12 cycles of KRD treatment (90% vs 72%).

Results concerning tandem transplant are controversial. In the EMN02 trial, after a short VCD induction, HR patients clearly benefited from the tandem ASCT. Indeed, tandem ASCT was able to overcome the adverse prognosis of HR cytogenetics (3-year PFS: 76% vs 69%; p = 0.48). By contrast, in the STAMINA trial, no benefit in terms of PFS was found with tandem ASCT. Although tandem ASCT is still considered a standard for HR disease in most EU centers, the benefits of this approach need to be reexamined in the setting of the most efficient quadruplet induction regimens. Similarly, the role of consolidation should be reviewed.

Regarding maintenance, although the recent UK Myeloma XI indicates a benefit from Lenalidomide maintenance, particularly in IMiD-sensitive patients, several studies, including the UK one, show that PFS and OS are still significantly shorter in HR as...
Table 1

Summary of most relevant efficacy data of current approaches for the treatment of newly diagnose and relapse MM. Results are split in high-risk (defined as del (17p), t (4;14) or t(14;16) and standard risk patients when available.

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<tr>
<th>NDMM – Trasplicable patients</th>
<th>NDMM – Non transplantable patients</th>
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<td><strong>VRD – GEM</strong></td>
<td><strong>SWOG trial (VRd vs Rd)</strong></td>
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<td><strong>CASSIOPEIA</strong> (Dara-VTD vs VTD)</td>
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<td><strong>PFS, m</strong></td>
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<td><strong>PFS, m</strong></td>
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<td><strong>ORR rate (%)</strong></td>
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Compared to standard-risk (SR) patients. Some studies showed the efficacy of Bortezomib in HR patients, but these do not distinguish the pure maintenance phase. Ixazomib maintenance has shown similar results in high and standard risk patients with a median PFS improvement of 5 months. Given these conflicting results, our policy in HR patients is to combine Lenalidomide with PIs, instead of using only a single agent.

In HR non-transplant candidates, treatment selection is clearly influenced by the degree of frailty, but here we will focus on fit patients in whom the goal should also be to achieve MRD negativity. The combinations of first-generation novel agents (VMP; VMP/VTP with VT maintenance or Len-Dex), have improved the response rate of HR patients, although their survival remains significantly inferior to that of SR patients. An ITM study of 1095 elderly patients showed that HR patients were associated with poor outcome, regardless of the treatment received. The combination of a proteasome inhibitor plus an IMiD (VRD) may yield better PFS but still cannot overcome the adverse prognosis of HR. Probably KRD may be a preferable option in this setting, although no randomized data is yet available. The information from monoclonal antibodies is still immature, nevertheless results from two Daratumumab-based trials (Dara-VMP and Dara-Rd) show that the PFS for HR patients is superior to that of the control arms, but still shorter as compared to SR patients. Probably, the combination of VRD+ anti-CD38 monoclonal antibodies, would be a preferred option and this is being evaluated in different phase III trials (IMROZ trial -Isatuximab VRD – ; CEPHEUS trial -Daratumumab VRD); but not data has been published yet.

In the relapse setting, we are currently dividing HR patients into Lenalidomide (Len)-naïve/sensitive and Len-refractory patients. In the first group, the combination that afforded the longest PFS was Dara-Len-Dex (POLLUX) (26.8 months), although this PFS was almost half of that reported for SR patients. Other Len-Dex combinations with Carbfilzomib (ASPIRE), Ixazomib (TOURMA-LINE), and Elotuzumab (ELOQUENT) yielded shorter PFS, but the differences between HR and SR patients were less pronounced. Information about Dara-VD is scarce in Len-refractory patients, but it is probably suboptimal. Interestingly, two phase-3 Pomalidomide-based regimens (Poma-VD and Isatuximab-PomaD), showed benefit for HR and perhaps could overcome the adverse prognosis of HR cytogenetics. Another, interesting combination with efficacy in HR patients is Dara-KRD, however, this quadruplet has only been evaluated in clinical trials and is not yet approved in the EU.

**Note:**
- **VRD – GEM** = Daratumumab, bortezomib, lenalidomide, dexamethasone, KRD = Daratumumab, lenalidomide, dexamethasone, VRD = Daratumumab, bortezomib, lenalidomide, dexamethasone, DVMP = Daratumumab, bortezomib, mephalan, prednisone, VPD = Daratumumab, bortezomib, lenalidomide, dexamethasone.
- **CR rate** = Post-induction CR rate.
- **MRA neg (%)** = MRD at data cut-off.
- **PFS, m** = Progression free survival.
- **ORR rate (%)** = Intention-to-treat.
- **KRD** = Carbfilzomib, lenalidomide, dexamethasone, KRd = Carbfilzomib, lenalidomide, dexamethasone, KRD-T = KRD followed by autologous stem cell transplant (ASCT), M = months, MRA = minimal residual disease, MM = not reported, ORR = overall response rate, PFS = Progression free survival, Post-ind = post-induction, PR = Partial remission, MRD = Minimal residual disease, NDMM = Not otherwise specified, POVM = Pomalidomide, VPD = Pomealidomide, VRD = Bortezomib, dexamethasone, VRD-GEM = Bortezomib, lenalidomide, dexamethasone, Spanish myeloma group schema, VTD = Bortezomib, thalidomide, dexamethasone.
- **CRD** = Complete remission, Dara-VTD = Daratumumab, bortezomib, thalidomide, dexamethasone, Dara-VD = Daratumumab, lenalidomide, dexamethasone, Dara-VMP = Daratumumab, bortezomib, melphalan, prednisone, Dara-VRD = Daratumumab, bortezomib, lenalidomide, dexamethasone.
- **KDR** = Carbfilzomib, lenalidomide, dexamethasone, KRD = Carbfilzomib, lenalidomide, dexamethasone, KRD-T = KRD followed by autologous stem cell transplant (ASCT), M = months, MRA = minimal residual disease, NR = not reported, ORR = overall response rate, PFS = Progression free survival, Post-ind = post-induction, PR = Partial remission, MRD = Minimal residual disease, NDMM = Not otherwise specified, POVM = Pomalidomide, VPD = Pomealidomide, VRD = Bortezomib, dexamethasone, VRD-GEM = Bortezomib, lenalidomide, dexamethasone, Spanish myeloma group schema, VTD = Bortezomib, thalidomide, dexamethasone.
- **VRD – GEM** = Daratumumab, bortezomib, lenalidomide, dexamethasone, Dara-VD = Daratumumab, lenalidomide, dexamethasone, VRD = Daratumumab, bortezomib, dexamethasone, DVMP = Daratumumab, bortezomib, mephalan, prednisone, VPD = Daratumumab, bortezomib, lenalidomide, dexamethasone.
- **CR rate** = Post-induction CR rate.
- **MRA neg (%)** = MRD at data cut-off.
Little or no information has so far been reported about the efficacy of new drugs, or combinations of them, in other challenging HR scenarios such as extramedullary disease, PC leukemia, early relapse, or primary refractory disease. In these patients, and not only in those with HR cytogenetics, treatment should be adapted to eradicate all malignant cells (MRD) and, in this context, innovative therapies, such as those involving CAR-T cells, antibody drug conjugates (such as Belantamab-Mafodotin) or T-cell engager antibodies, should be explored early in the course of the disease. Indeed, some trials evaluating these strategies in earlier lines of therapy and high-risk disease are already ongoing.

References


Update revision on definition and treatment of high-risk patient


In this article importance of depth of response and particular achievements of MRD negativity is discussed based on results from Pooled analysis of all PETHEMA/GEM clinical trials.


Important study since this is the first Pomalidomide-based combination with anti-CD38 monoclonal antibody reported.