Treatment of High-Risk Multiple Myeloma: A Case Study From Induction to Maintenance

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Case Summary: A 49-year-old man initially presented with low back pain, and computed tomography (CT) imaging revealed many osteolytic bone lesions that were hypermetabolic by positron emission tomography (PET). His laboratory values were as follows: M-spike 1.3 g/dL IgG Kappa, hemoglobin 16.1 g/dL, serum creatinine 0.9 mg/dL, calcium 10.0 mg/dL, albumin 5.1 g/dL, beta 2 microglobulin 3.3 mg/L, and lactic dehydrogenase (LDH) 179 U/L. Urine studies were negative for monoclonal protein. A bone marrow biopsy revealed 10% monotypic kappa-restricted plasmacytosis, and he was diagnosed with multiple myeloma (MM). Cytogenetics performed by fluorescent *in situ* hybridization revealed gain of chromosome 1q and *TP53* deletion. The patient was categorized as International Staging System (ISS) stage 1 and Revised-ISS stage 2.

Treatment Approach: The patient was determined to have high-risk disease based on the presence of 1q gain and *TP53* deletion. He initiated induction therapy with carfilzomib, lenalidomide, and dexamethasone (KRd). He achieved an imaging plus minimal-residual disease (MRD)-negative stringent complete response by PET/CT and flow cytometry (depth 10^{-5}). He then proceeded with high-dose melphalan and autologous stem cell transplant (ASCT); post-ASCT day +80 imaging and bone marrow biopsy confirmed a continued imaging plus MRD-negative stringent complete response. After discussion regarding post-transplant options, the patient proceeded with extended KRd consolidation.

Discussion: The main presentation points by Drs. Derman and Jasielec focused on the entity of high-risk MM, including: 1) its evolving definition, 2) induction treatment strategies 3) the role of autologous and allogeneic transplant, and 4) post-transplant strategies.

***Evolving Definitions of High-Risk Multiple Myeloma*.** The ISS is a simple risk stratification tool that uses the serum β2-microglobulin and albumin to stratify MM patients into one of three stages.[1] The revised-ISS (R-ISS) improved prognostication and risk stratification by incorporating the measures of disease biology such as LDH and high-risk cytogenetics including t(4;14), t(14;16), and 17p deletion (*TP53)*.[2] The International Myeloma Working Group (IMWG) created parallel risk stratification criteria that used age and cytogenetics.[3] High-risk cytogenetic abnormalities (CA) in MM include: t(4;14), t(14;16), t(14;20), 1q gain, and 17p deletion (*TP53).*[4–7] However, there is substantial heterogeneity among patients with MM harboring high-risk CA.[7–9] As a result, gene expression profiling (GEP) has garnered interest as a way to resolve this heterogeneity; however, these are not currently employed as part of the standard-of-care.

Induction Treatment Strategies for High-Risk Multiple Myeloma. For high-risk MM, the 2016 IMWG consensus guidelines for management of MM with high-risk cytogenetics endorsed triplet therapy induction with a proteasome inhibitor, immunomodulatory drug, and dexamethasone.[5] Few randomized trials support induction with this triplet, and data on outcomes of high-risk patients is limited to subgroup analysis. The results of the SWOG S0777 study showed superior PFS and OS for newly diagnosed MM patients receiving bortezomib, lenalidomide, and dexamethasone (VRd) vs Rd. In a subset analysis of high-risk patients, there was a trend toward superior PFS in the VRd arm, though it did not reach significance.[10] An interim analysis of the IFM-2009 study, which compared the efficacy of VRd followed by early ASCT and lenalidomide maintenance versus VRd

followed by lenalidomide maintenance with ASCT deferred until first relapse, showed a 9 month PFS benefit for those with standard-risk CA who underwent early transplant, but not in the subgroup of patients with high-risk CA.[11] Notably, the patients with high-risk CA who achieved MRD-negativity at a depth of 10^{-6} by next generation sequencing (NGS) after one year of lenalidomide maintenance had comparable PFS to those patients with standard-risk CA who were MRD-negative, regardless of treatment arm.[12] The abrogative effect of MRD-negativity on high-risk CA has been demonstrated in a few other studies as well,[13] suggesting that the goal for treatment in high-risk MM should be MRD-negativity.

Several studies have generated promising data for the use of carfilzomib (K) in the front-line setting for MM. The phase 2 MM Research Consortium trial investigating a total of 18 cycles of KRd delivered over the span of induction, consolidation, and maintenance after ASCT, showed that 72% of patients, both standard and high-risk, achieved MRD-negative CR by NGS. Three-year PFS was also comparable among both standard- and high-risk patients (93% vs 87%).[14] In the phase 3 FORTE trial, an approximate 50% MRD-negative CR by NGS was achieved among patients with high-risk MM whether they were randomized to receive KRd followed by ASCT and then KRd maintenance arm or to 12 cycles of KRd alone, but fewer patients with high-risk MM had early relapse in the transplant arm (12 pts [8%] vs 26 pts [17%]; *P*=0.015).[15] The ongoing ENDURANCE and COBRA trials are comparing VRd and KRd head-to-head, but may not be powered to demonstrate a difference in high-risk MM.

The role for quadruplets in high-risk MM is yet to be determined. Thus far, no survival difference has been demonstrated with a quadruplet regimen over a triplet in high-risk MM. The phase 3 Myeloma XI (Carfilzomib, cyclophosphamide, lenalidomide, dexamethasone), ALCYONE (Daratumumab, bortezomib, melphalan, prednisone), GRIFFIN (Dara/VRd), or CASSIOPEIA (Dara/VTd) studies have shown a survival advantage to quadruplets over their triplet comparator arms.[16–19] Lack of power to detect a difference in high-risk MM remains an issue.

Role of Transplant in High-Risk Multiple Myeloma. High-dose melphalan (140-200 mg/m^2) followed by ASCT has been the standard of care for most newly diagnosed transplant-eligible MM patients. However, the role of ASCT in high-risk MM is limited to subset analyses. The IFM-2009 study was not able to demonstrate benefit to ASCT in the frontline setting for high-risk MM.[11] Early results from the FORTE trial suggest the opposite; patients who received KRd + ASCT had a lower rate of early relapse vs KRd alone, which was attributed mainly to lower relapse rate in those with R-ISS stage 2 and 3.[15] A phase 3 study comparing standard melphalan conditioning to a regimen of busulfan/melphalan found that the latter led to superior PFS, including in the high-risk subset.[20]

Tandem ASCT for high-risk MM remains controversial. Recent data – such as from the European EMN02/HO95 study – found a PFS and OS benefit for tandem ASCT over single ASCT;[21] however, patients received CyBorD induction which is no longer considered standard of care for most newly diagnosed MM patients in the United States. In contrast, the US-conducted STaMINA trial found no survival difference between single ASCT, single ASCT with four cycles of VRd consolidation, and tandem ASCT.[22]

Allogeneic SCT in MM is associated with high rates of transplant-related mortality predominantly due to graft versus host disease. Even high-risk MM studies have failed to show an OS benefit for tandem autologous/allogeneic SCT compared to tandem ASCT, though few patients with high-risk MM can achieve long-term remission.[23,24]

Post-Transplant Strategies in High-Risk Multiple Myeloma. Post-transplant options for high-risk MM include consolidation with multi-drug therapy and/or single-agent maintenance therapy. The consolidation arm in the STaMINA trial consisted of four cycles of VRd followed by lenalidomide maintenance, which did not lead to a survival benefit compared to maintenance alone or tandem ASCT followed by lenalidomide maintenance.[22] Nonrandomized phase 2 data has suggested that longer courses of VRd (up to three years) and KRd (14 cycles) consolidation lead to excellent outcomes in high-risk MM.[14,25] A meta-analysis of three randomized clinical trials evaluating lenalidomide maintenance vs placebo found that lenalidomide increased PFS and OS among all-comers but not in subset of patients with high-risk CA.[27] The Myeloma XI study was reported later, and concluded that lenalidomide maintenance led to superior OS in transplant-eligible patients only; in this case, the OS benefit extended to patients with standard-risk and some high-risk patients ($\geq$2 high risk CA).[28] Bortezomib maintenance appeared to abrogate the effect of 17p deletion and t(4;14) in the HOVON-65/GMG-HD4 study.[29] Although maintenance with ixazomib offers the convenience of an oral regimen, a phase 3 randomized clinical trial showed only a modest PFS advantage over placebo.[30]

Concluding Points: High-risk MM remains a heterogenous and evolving entity. While R-ISS incorporates t(4;14), t(14;16) and 17p deletion, IMWG criteria also recognizes t(14;20) and 1q gain as high-risk CA; gene expression profiling assays are in development and may offer additional insight into the heterogeneity of high-risk MM. Standard of care induction for NDMM with high-risk CA should consist of proteasome inhibitor, immunomodulatory drug, and dexamethasone triplet. Data on quadruplet regimens adding monoclonal antibodies to this backbone are emerging. Transplant-eligible patients with high-risk MM should undergo ASCT and consideration could be given to tandem transplant in a patient with suboptimal response to proteasome-inhibitor–based induction. The goal of treatment should be to achieve and maintain MRD-negative CR. In phase 3 randomized trials, maintenance with bortezomib or lenalidomide has been proved to improve PFS. However, in phase 2 studies, extended consolidation/maintenance with VRd or KRd have shown to yield even longer PFS.

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