Management of Newly Diagnosed Multiple Myeloma Based on Risk Stratification

Presented by Natalie S. Callander, MD

ABSTRACT

In the context of newly diagnosed multiple myeloma, recent advances in risk assessment have influenced treatment decisions and paved the way for more individualized approaches. The current NCCN Guidelines for Multiple Myeloma outline the updated staging system, highlight various high-risk features for disease progression/relapse, and provide evidence-based recommendations for myeloma therapy. Although the therapeutic landscape continues to shift toward increased risk adaptability, ongoing efforts should place an emphasis on tackling modifiable risks.

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“Despite newer therapies, outcomes for our highest-risk patients with multiple myeloma are still not optimal,” commented Natalie S. Callander, MD, Professor of Medicine, University of Wisconsin School of Medicine and Public Health, and Director of the Myeloma Clinical Program, Carbone Cancer Center, and Vice Chair of the NCCN Guidelines Panel for Multiple Myeloma. At the NCCN 2023 Annual Congress: Hematologic Malignancies, she highlighted the risk assessment strategies and clinical trial data that may aid in the development of individualized treatment approaches for patients with newly diagnosed multiple myeloma.

Revisiting the Risk Stratification System

Although the International Staging System (ISS) was favored for its simplicity of use, requiring just 2 laboratory values—beta-2 microglobulin and albumin—Dr. Callander explained that responses within its intermediate-risk category were variable. “So, in 2015, the revised (R)-ISS came out, which incorporated lactate dehydrogenase [LDH] … and high-risk cytogenetics, namely, t(4;14), t(14;16), and p53 deletion,” she commented. “Currently, this doesn’t seem to be enough, and we’ve been able to show that there are a number of other abnormalities we need to take into account.”

The updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Multiple Myeloma outline factors considered as high risk for disease progression or relapse in patients with newly diagnosed disease.1 Dr. Callander particularly highlighted the significance of R-ISS stage III disease; extramedullary presentation; circulating plasma cells; and other cytogenetic abnormalities, such as t(14;20), del(1p32), gain and/or amplification of 1q21, and MYC translocations, and high-risk gene expression profiles as high-risk factors of disease progression in those with newly diagnosed multiple myeloma.

Using Risk in Decision-Making for Transplant-Eligible Patients

“Almost every study since 1996 has shown that the addition of ASCT [autologous stem cell transplantation] improves progression-free survival [PFS] and often overall survival [OS],” commented Dr. Callander. “[Nevertheless], this conclusion has come under attack.”

The DETERMINATION trial demonstrated the superiority of ASCT-based first-line therapy with respect to PFS.2 However, she stated, “There wasn’t an OS advantage reported at 76 months of follow-up, [and] some individuals have interpreted this transplantation as… not being very useful.” According to Dr. Callander, such a conclusion may be “short-sighted.” Although the addition of ASCT appeared less effective for high- versus standard-risk disease, she noted, those harboring risk-associated markers who underwent this procedure nevertheless experienced a 4-fold improvement in PFS.

“I think [these data] really underscore that this group of patients definitely need a transplant,” Dr. Callander remarked. She noted that, although the FORTE trial evaluated a different selection of regimens, it yielded a similar conclusion.3

Using Measurable Residual Disease to Assess or Modify Risk

“We have known for a number of years that, no matter what the treatment was initially, if patients became measurable residual disease [MRD]–negative, they had better outcomes than if they were MRD-positive,” commented Dr. Callander. “We are starting to get some hints about whether any
specific interventions will increase the proportion of patients who become MRD negative.”

Based on the final analysis of the GRIFFIN trial, rates of MRD-negativity favored a 4- versus 3-drug induction regimen.4 This trend seemed to correlate with the 4-year PFS rates (87.2% vs 70.0%, respectively).

In the MASTER trial, MRD assessments guided the continuation or cessation of posttransplant consolidation therapy.5 This strategy continuously improved the rates of MRD negativity in all-comers, as well as in both the standard- and high-risk cytogenetic subgroups, according to Dr. Callander. “[However], what we ended up finding later on is that those highest-risk patients, such as those with ≥2 cytogenetic changes, did not do as well with this strategy. This, we think, is a signal that [these patients are] going to need something additional,” she explained. “Even though [patients from the GRIFFIN trial] had a longer [duration of] maintenance therapy, the same phenomenon exists.” In the proposed MASTER-2 trial, all postinduction treatment decisions will thus be made via an MRD response–adapted strategy (ClinicalTrials.gov identifier: NCT05231629).

The MUKnine OPTIMUM trial was conducted to determine whether these ultra–high-risk patients with either double-hit myeloma, a high SKY92 gene profiling signature, or primary plasma cell leukemia may benefit from intensive treatment with multiple agents during the induction, ASCT, consolidation, and maintenance phases. Based on a comparative analysis,6 Dr. Callander stated that “They feel they’re doing better” than high-risk patients from the contemporaneous Myeloma XI trial who underwent standard treatment, but these data are preliminary.

**Advances in the Treatment of Elderly Populations**

Although the majority of patients with multiple myeloma are aged ≥65 years, according to Dr. Callander, “There is a paucity of trials to [consult] … to figure out the best way to treat them.” The MAIA and IFM2017-03 trials address this gap.

The MAIA trial established the use of combination daratumumab + lenalidomide/dexamethasone (DRd) for patients who are transplant-ineligible due to their age (≥65 years) or comorbidities.7 Compared with lenalidomide/dexamethasone (Rd) alone, this combination was found to nearly double the median duration of PFS (61.9 vs 34.4 months).8 With a “striking” 60-month OS rate (66.6% vs 53.6% with Rd), Dr. Callander emphasized that the DRd regimen “[sets] the bar to meet.” Lenalidomide + bortezomib/dexamethasone (RVd)–lite will be evaluated as a contender for frail or patients aged >65 years in the SWOG 2209 trial (ClinicalTrials.gov identifier: NCT05561387).

IFM2017-03 was designed to evaluate whether dexamethasone may be limited in elderly frail patients. Based on preliminary data, daratumumab/lenalidomide (DR) versus dose-adjusted Rd resulted in a significantly higher objective response rate (96% vs 85%; P = .001).9

**Role of Maintenance Therapy**

“In the Myeloma XI trial, regardless of your risk categorization, the addition of lenalidomide maintenance [therapy] helped in terms of disease progression, but the benefit is less if you had double-hit myeloma,” explained Dr. Callander. Although there have since been several attempts to determine whether maintenance therapies may change outcomes in this population, she thinks “There is more to come for this difficult to treat group of patients.”

The results of the DRAMMATIC trial will be of particular interest, Dr. Callander noted, as they may elucidate the optimal duration of maintenance therapy based on MRD status (NCT04071457). “[However], because it’s powered for survival, it is going to be a while before we know what the outcomes are.”

**Managing Modifiable Risks**

“[Based on the results of the CoMMpass trial], there are 2 things that stood out as leading to lower OS for Black patients,” Dr. Callander explained. “One was access to triplet therapy, and the other was access to transplants.”

In a study of the simultaneous treatment of different racial groups via a retrospective review of veterans treated through the VA Health Care System, where access is equivalent, both Black patients and Black patients aged <65 years demonstrated superior OS outcomes compared with their White counterparts.10 “[These data further] underscore how important access to care is,” she added.

Although corticosteroids are the most commonly administered class of drugs in patients with multiple myeloma, Dr. Callander recommended minimizing their use to mitigate the risk of developing steroid-induced adverse effects. In terms of supportive care measures for those experiencing other complications, adhering to the NCCN Guidelines may reduce the associated risks and “Make a difference in how patients do in the long run” (Figure 1).1

**Case Presentations**

The first case focused on a 43-year-old female who was found to have an IgG spike and elevated lambda light chains. Although PET imaging did not reveal lytic lesions, diffuse marrow involvement was detected. Bone marrow biopsy showed 30% plasma cells, and fluorescence in situ hybridization (FISH) identified t(4;14). Her disease was classified as R-ISS stage II.

The patient did not want to undergo ASCT; consequently, she was enrolled in the ongoing EQUATE trial and randomly assigned to receive DRd without the addition of bortezomib. According to Dr. Callander, after having undergone 18 cycles of such induction therapy, the
patient is currently MRD-negative and responding well to maintenance therapy with DR.

The second case featured a 77-year-old male who presented with a pathologic fracture of the right femur. Upon examination, a number of hematologic abnormalities were documented, including anemia, high total protein levels, low albumin levels, and an IgG level of 8,116 mg/dL. The patient underwent a bone marrow biopsy, which revealed 90% plasma cells.

FISH confirmed the presence of p53 deletion and a 1q amplification. “Even before we knew these cytogenetics, based on his LDH and beta-2 [microglobulin] alone, [his disease was classified] into the R-ISS III category,” Dr. Callander remarked.

She chose a 4-drug regimen comprising daratumumab/lenalidomide/bortezomib/dexamethasone (D-Rvd). However, given the patient’s age, Dr. Callander limited the administration of the latter 2 agents. Upon completion of this induction therapy, he will undergo ASCT.

Disclosures: Dr. Callander has disclosed no relevant financial relationships.

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References