Managing Myeloma

Advances and Evolving Standards of Care in Transplant-ineligible NDMM

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Welcome to this issue on outlining practical strategies for implementing new and evolving standards of care into the treatment of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). We will summarize the clinical data that supports the use of triplet and quadruplet regimens in patients with NDMM and correlate patient or disease characteristics with appropriate triplet or quadruplet regimens in transplant-ineligible disease. We will go on to identify factors to consider when developing an optimized treatment sequencing strategy for an individual transplant-ineligible NDMM patient.

Distilling data in frontline treatments and emerging standards of care for patients with NDMM

Multiple myeloma is a systemic plasma cell malignancy. There were almost 35,000 NDMM cases and around 12,000 deaths in the year 2021, and this incidence continues to grow.[1,2] However, the percentage of patients who are surviving the disease beyond five years has more than doubled in the last two decades and currently stands at about 55.6%.[3] The overall median age of diagnosis is 69 years but is slightly younger in Black adults.[3] Multiple myeloma is more common in men and is the most common hematologic malignancy in the Black population, where it tends to present at an earlier age.[3] Myeloma is not one disease. There are between six to eight subgroups, depending on how they are defined. Genomic changes are present from the monoclonal gammopathy of undetermined significance (MGUS) stage onward. The MGUS to active myeloma transition occurs at different time points in different patients and depends on the interaction of the myeloma cells with the bone marrow microenvironment.[4,5] Patients with NDMM have different degrees of end-organ damage during their journey of MGUS to active myeloma.[4,5]

The management strategies and new therapies have improved multiple myeloma survivorship from a median of 2-3 years to over 10 years during the last two decades.[4,5] For an optimal response and survival outcome, studies have revealed that the right strategy is extremely important during the first year following diagnosis.[4,5] We have used the same treatment paradigm for almost two decades, however, this will change as newer cellular therapies and bispecific antibodies become available.

Today, newly diagnosed patients are categorized as either transplant-ineligible or eligible. The goal of initial induction therapy is to get patients into as deep a response as possible, with or without stem cell transplantation, and then move to the maintenance phase, which is geared towards maintaining that response. Supportive care is also required through the management of bone health, infection risk, pain management, and overall well-being in patients with NDMM. If

the disease recurs, patients are de-staged and reassessed to find the best available strategy at that point in time.

The management plan for patients with NDMM is also dynamic during the early stages of the disease, with treatment being continuously reassessed and updated as required. A multidisciplinary approach is common in older patient populations, which is typical in NDMM. The treatment plan includes monitoring the treatment response along with the safety and adverse event (AE) profile, while continuously making changes when necessary.

Management of transplant-ineligible multiple myeloma patients

We will likely not classify NDMM as transplant-eligible or ineligible in the next 2-3 years due to emerging data. However, we may replace this classification with eligible or non-eligible T-cell-directed therapy. Bispecific T-cell engagers and chimeric antigen receptor T-cell therapy (CAR T) are both being used in the NDMM transplant-ineligible setting. Transplant ineligibility is confirmed by the presence of comorbidities and the patient's performance status to the three-drug combinations. Either RVd lite [a 35-day cycle of lenalidomide (15 mg, days 1-21) plus bortezomib (1.3 mg/m^2 weekly subcutaneously on days 1, 8, 15, and 22), and dexamethasone (20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 for patients ≤75 years, and days 1, 8, 15, and 22 for those >75 years)] for 8 to 12 cycles or until response plateau before patients move on to maintenance treatment.[6] Patients who have standard-risk disease only take lenalidomide.[7] In high-risk disease, the proteasome inhibitor (PI) maintenance, bortezomib, is given in addition to lenalidomide.[8] Then, for patients who start off on the daratumumab-based triplet regimen, DRd (daratumumab + lenalidomide + dexamethasone), we continue this treatment.[9] Once patients have had a response plateau, the regimen may be tweaked or one of the drugs discontinued, depending on the patient's specific situation.[8]

The RVd (lenalidomide + bortezomib + dexamethasone) data comes from the SWOG777 study, a phase III trial, which compared RVd to Rd (lenalidomide and dexamethasone) as induction therapy for patients without immediate intent for stem cell transplant.[10] This study showed superiority of the PI/immunomodulatory drug (IMiD) induction compared to just Rd induction for both progression-free survival (PFS) and overall survival (OS).[10] Although the median age in SWOG777 was 63, it validated the use of a three-drug combination for NDMM in the transplant-ineligible as well as eligible settings.[10]

The RVd lite regimen is used in many older patients and was developed at Massachusetts General Hospital Cancer Center by Elizabeth O'Donnell, MD, and Noopur Raje, MD. They used a single-arm study with a lower 15 mg dose of lenalidomide, and weekly dosing of bortezomib in an older patient population with a median age of 73 years.[6] Results revealed similar response rates and PFS to SWOG777. The safety data showed good tolerability, even though around two-thirds of the patients had reversible grade 1 and 2 peripheral neuropathy.[6]

The DRd combination was an important and relevant study in the older patient population. This regimen was approved three years ago based on the phase III MAIA trial that compared the DRd drug combination to Rd, which at that time was the standard of care for this patient population.[9] These patients were an older transplant-ineligible cohort with a median age of 73.[9] Overall response rates (ORR) with DRd was 93% with a high proportion of patients getting a significant partial response or better.[9] The ORR was still 81% at close to the five-year follow-up

mark.[9] At the 56-month median follow-up, the median PFS was not reached for DRd, whereas it was 34.4 months for Rd.[9] The median OS had not been reached in either arm at the 56-month follow-up.[9] It was statistically significant in favor of DRd at that mark with a hazard ratio of 0.68, demonstrating that DRd is an effective regimen.[9] Because the median PFS is still not reached, this will be a challenging benchmark for the other clinical trials evaluating patients in this population.

The CEPHEUS trial, which is fully enrolled, is testing the combination of a PI, an anti-CD38 monoclonal antibody, lenalidomide, and dexamethasone in an older patient population (quadruple therapy).[11] CEPHEUS compared the combination of daratumumab with RVd as part of induction therapy versus RVd induction therapy alone, followed by Rd in both arms.[11] Effectively, this study is comparing the SWOG777 regimen versus SWOG777 plus daratumumab and will look at possibly incorporating daratumumab into the frontline setting.

Another anti-CD38 monoclonal antibody, isatuximab, is being studied in the IMROZ trial. This study uses isatuximab plus RVd, then maintenance is continued with isatuximab, lenalidomide, and dexamethasone until relapse or progression.[12] The standard of care arm in this study is the SWOG777 regimen. These trial results will be important for the global myeloma community.

Finally, the CARTITUDE-5 trial is testing RVd as induction therapy, followed by Rd maintenance versus SWOG777 as the standard of care arm.[13] An experimental arm gave anti-B-cell maturation antigen antibodies (BCMA)-directed CAR T-cell therapy, cilta-cel, after the RVd induction treatment.[13] BCMA-directed CAR T-cell therapy is quite active in both late relapse and early relapsed multiple myeloma. Results from these trials will influence our approach to transplant-ineligible NDMM over the next few years.

Many programs are beginning to incorporate comprehensive geriatric assessments and partnering with their geriatric-oncology colleagues in evaluating older, frail myeloma patients. Tanya Wildes, MD, of the University of Nebraska Medical Center has been a champion for older myeloma patient care, where she and her colleagues evaluate patients with comprehensive geriatric assessments, and then utilize those attenuated regimens in those patients. We are also seeing some clinical trials emerge through the US cooperative group mechanism.

Amrita Krishnan, MD, Professor of Medicine at the City of Hope in Los Angeles emphasized that getting the resources and support to perform geriatric assessments is challenging and like many geriatric oncology units across the US, the City of Hope geriatric oncology unit is still a work in progress. While much headway has been made over the last two decades in the treatment landscape of transplant-ineligible NDMM, more work is needed to increase the number of geriatric oncology units across the country, and thereby alleviate the burden of NDMM in the older community.

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References:

1. National Cancer Institute website. Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ)-Healthcare Professional Version. Date updated February 2021. Date accessed May 2021. http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional#Section_4
2. American Cancer Society website. Myeloma. Date accessed May 2021. https://cancerstatisticscenter.cancer.org/?_ga=2.47184933.325832967.1600196335-611855784.1581698489#!/cancer-site/Myeloma
3. National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) website. Date accessed May 2021. http://seer.cancer.gov/statfacts/html/mulmy.html.
4. Martinez-Lopez J, Blade J, Mateos MV, et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. *Blood*. 2011;118(3):529-534. doi:10.1182/blood-2011-01-332320
5. Usmani SZ, Nair B, Qu P, et al. Primary plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling and clinical outcome with total therapy protocols. *Leukemia*. 2012;26(11):2398-2405. doi:10.1038/leu.2012.107
6. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol*. 2018;182(2):222-230. doi:10.1111/bjh.15261
7. Larocca A, Salvini M, De Paoli L, et al. Efficacy and Feasibility of Dose/Schedule-Adjusted Rd-R Vs. Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase III Randomized Study. *Blood* 2018; 132 (Supplement 1): 305. doi:https://doi.org/10.1182/blood-2018-99-111796
8. Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. *Lancet Haematol*. 2021;8(1):e45-e54. doi:10.1016/S2352-3026(20)30354-9
9. Facon T, Kumar SK, Plesner T, et al. Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA). *Blood* 2018; 132 (Supplement 1): LBA–2. doi:https://doi.org/10.1182/blood-2018-120737
10. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527. doi:10.1016/S0140-6736(16)31594-X
11. Zweegman S, et al. ASCO 2019. Abstract TPS8066. ClinicalTrials.gov Identifier: NCT03652064. Date accessed February 2022.
12. Orlowski RZ, et al. ASCO 2018. Abstract TPS8055.; ClinicalTrials.gov Identifier: NCT03319667. Date accessed July 2021.
13. Janssen Research & Development, LLC. ClinicalTrials.gov Identifier: NCT04923893. Date accessed January 2023.

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