Updates in the Treatment of Multiple Myeloma

Presented by Shaji K. Kumar, MD

ABSTRACT

The treatment of multiple myeloma is marked by many recent advances, but for newly diagnosed patients the standard of care for induction remains the combination of a proteasome inhibitor, immunomodulatory drug, and dexamethasone. The role of a 4-drug induction regimen is still being defined, but can be considered for patients with high-risk disease. For patients who are eligible to undergo stem cell transplant, this approach remains the preferred option, but transplant can be delayed until relapse if patients prefer. In those who are not eligible for transplant, based on impressive data with daratumumab/lenalidomide/dexamethasone, this triplet should be considered as initial therapy. In patients with relapsed disease, it is important to switch treatment to new drug classes; for this, multiple combinations can be recommended. Updated guidelines now include new drugs for refractory disease: selinexor and belantamab mafodotin, both listed as “other regimens” in the NCCN Guidelines, can be considered.

J Natl Compr Canc Netw 2021;19(5.5):648–651
doi: 10.6004/jnccn.2021.5009

The treatment paradigm for multiple myeloma continues to evolve at a rapid pace, with the recent introduction of several new drugs and with changing concepts in terms of treatment goals, according to Shaji K. Kumar, MD, Professor of Medicine and Medical Director, Cancer Center Research Office, Mayo Clinic Cancer Center, at the NCCN 2021 Virtual Annual Conference, who guided listeners through the expanded list of treatments options and their supportive data. “We want to arrive at an accurate diagnosis for patients with active myeloma that needs treatment, and to incorporate risk stratification, which is critical in terms of deciding upon the overall treatment goals and approaches over time.... Unfortunately, patients continue to relapse. We have to come up with new treatment approaches to maintain control over a long period of time.”

Monoclonal Gammopathies of Clinical Significance

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Multiple Myeloma outline the essential aspects of the diagnostic workup—in particular, measurement of tumor burden and end-organ damage—and suggest additional tests for certain situations that help distinguish myeloma from other related disorders.¹

The updated guidelines have added several pages devoted to monoclonal gammopathies of clinical significance, including those of renal significance (MGRS) and neurological significance (MGNS). When MGRS is suspected (renal dysfunction in the context of monoclonal protein), detailed workup includes renal biopsy, with

findings confirmed by electron microscopy and immunofluorescence staining. Thorough workup for suspected MGNS, as well, can help delineate the underlying plasma cell disorder and identify specific abnormalities, such as anti-MAG antibodies. “Based on the severity and tempo of the disease, some of these patients can be watched closely, while others may need therapy along the lines of myeloma,” he said.

Standard of Care for Induction

Bortezomib/lenalidomide/dexamethasone (VRd) remains the standard of care in newly diagnosed patients, regardless of whether they are eligible for hematopoietic stem cell transplant (HSCT) or not. Attempts have been made to improve upon VRd as initial therapy.

The phase III ENDURANCE study sought to improve upon VRd by replacing bortezomib with the next-generation proteasome inhibitor carfilzomib (KRd), but determined that there was no progression-free survival (PFS) advantage (hazard ratio [HR], 1.04; $P=.742$).² As a result, VRd remains the recommended initial therapy in patients with newly diagnosed disease.

The CASSIOPEIA trial did find a significant improvement in PFS with the addition of the monoclonal antibody daratumumab to bortezomib/thalidomide/dexamethasone (D-VTd) (HR, 0.47; $P<.0001$),³ but thalidomide is rarely used in the United States. In 2020, the more relevant phase II GRIFFIN trial⁴ found the addition of daratumumab to VRd (D-VRd) for induction and consolidation, with daratumumab/lenalidomide continued as maintenance, led to deeper responses: complete responses or

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES
Preferred Regimens <ul style="list-style-type: none"> • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone^e
Other Recommended Regimens <ul style="list-style-type: none"> • Carfilzomib/lenalidomide/dexamethasone • Daratumumab^f/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone^g • Ixazomib/cyclophosphamide/dexamethasone^g • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab^f/cyclophosphamide/bortezomib/dexamethasone • Daratumumab^f/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib^h (VTD-PACE)
MAINTENANCE THERAPY
Preferred Regimens <ul style="list-style-type: none"> • Lenalidomideⁱ (category 1)
Other Recommended Regimens <ul style="list-style-type: none"> • Ixazomib (category 1) • Bortezomib
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/lenalidomide

Figure 1. Primary therapy for transplant candidates from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Multiple Myeloma. Version 4.2021. To view the most recent version, visit [NCCN.org](https://www.nccn.org).

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better in 81.8% of those in the D-VRd arm versus 60.8% in the RVd arm ($P=.0014$). Furthermore, 63.6% versus 47.4% of patients, respectively, achieved minimal residual disease (MRD) negativity ($P=.0253$).

“While PFS and overall survival [OS] data from this study are awaited, the standard induction approach is still the triplet of a proteasome inhibitor and immuno-modulatory drug [IMiD] in the transplant setting,” Dr. Kumar said. “But there are certain settings, such as high-risk disease, where 4-drug regimens may be appropriate, given that they are associated with higher MRD negativity—a characteristic that often appears to improve outcomes of high-risk patients.”

Is Up-Front Transplant Still Preferred?

Myeloma experts still wrestle with the necessity of performing HSCT as primary therapy versus delaying until relapse. The 2017 IFM 2009 trial⁵ clearly showed a 12-month improvement in PFS for immediate HSCT following VRd induction (HR, 0.70; $P=.0001$). Long-term follow-up, however, has not shown a difference in OS or time to second progression, which is important because 77% of patients in the nontransplant arm did undergo a transplant at relapse. These results suggest that even with effective induction therapy, transplant still has a role. It can, however, be delayed to time of relapse without compromising OS, thereby providing more choices for patients, Dr. Kumar commented.

The NCCN Guidelines for primary therapy continue to list VRd as the preferred up-front regimen (category 1), but allow for many other options (Figure 1). In addition, the guidelines emphasize the importance of maintenance therapy, making lenalidomide a category 1 recommendation. For high-risk patients, bortezomib/lenalidomide can be recommended.

Newly Diagnosed Transplant-Ineligible Patients

Primary therapy for patients who are not candidates for HSCT, the addition of daratumumab to bortezomib/melphalan/prednisone has significantly improved response rates, PFS rates (HR, 0.42; $P<.0001$) and, importantly, OS rates (HR, 0.60; $P=.0003$) in the phase III ALCYONE trial.⁶ Because melphalan is rarely used in the United States, however, an IMiD-containing regimen is the more relevant backbone to be improved upon. To this end, at the 2020 ASH Annual Meeting, Dr. Kumar provided an update of the phase III MAIA study, reporting that the addition of daratumumab to lenalidomide/dexamethasone (D-Rd) led to a significant improvement in PFS⁷; median PFS was not reached, but was 51.3 months with Rd, and the 48-month PFS was projected at 60%. Similarly, in TOURMALINE-MM2,⁸ the addition of the oral proteasome inhibitor ixazomib to Rd led to a 14-month improvement in PFS, although this difference was not statistically significant (HR, 0.83; $P=.073$).

The guidelines for nontransplant candidates were updated based on the results of these trials. Preferred regimens with category 1 recommendations include VRd and D-Rd, which have both been shown to improve PFS, with VRd also showing improved OS. Lenalidomide + low-dose dexamethasone remains a category 1 option for older or frail patients. Additionally, bortezomib/cyclophosphamide/dexamethasone falls under the preferred category. Other combinations that include carfilzomib, ixazomib, or daratumumab can also be used as part of primary therapy. Maintenance with lenalidomide (category 1) remains important; bortezomib and bortezomib/lenalidomide are acceptable in some cases.

Relapsed Myeloma: A Rapidly Evolving Area

“The relapsed/refractory disease area is evolving, with even more new treatments, especially immunotherapies, which in the next 2 to 3 years will play major roles. However, they are not yet approved, and therefore not yet part of the guidelines,” Dr. Kumar said.

As is true for the early disease setting, many phase III trials have attempted to improve upon bortezomib-based regimens. Some have replaced bortezomib with carfilzomib or added panobinostat, daratumumab, or elotuzumab to bortezomib/dexamethasone. These approaches have all improved PFS and, in some cases, OS. Similarly, these drugs (as well as isatuximab) have been added to the backbone of lenalidomide/dexamethasone, also leading also to deepened responses and improvements in PFS.

Treatment of Lenalidomide-Refractory Relapsed Disease

“However, clinicians need to keep in mind that current treatment in the up-front setting often calls for lenalidomide maintenance until relapse, and as a result, many patients who present with first relapse are lenalidomide-refractory. This means many of these regimens may not be appropriate, as many studies excluded patients with lenalidomide-refractory disease,” Dr. Kumar pointed out.

Several phase III trials have evaluated the addition of a monoclonal antibody with a next-generation IMiD or proteasome inhibitor in populations that include lenalidomide-refractory disease. In fact, 3 trials added a monoclonal antibody to the backbone of pomalidomide/dexamethasone compared with pomalidomide/dexamethasone alone. In ICARIA,⁹ the addition of isatuximab improved response rates, depth of response, and PFS rates (HR, 0.596; $P=.001$), with a trend favoring OS (HR, 0.68; $P=.0631$). The APOLLO trial investigated the addition of daratumumab,

with improved PFS rates (HR, 0.63; $P=.0018$).¹⁰ Lastly, in ELOQUENT-3,¹¹ the addition of elotuzumab improved PFS (HR, 0.54; $P=.008$), with a trend toward improved OS (HR, 0.62). Thus, as evidenced by the data, any of these monoclonal antibodies are reasonable additions to pomalidomide/dexamethasone in patients with lenalidomide-refractory disease. Data from phase II studies also suggest these patients respond well to carfilzomib + pomalidomide/dexamethasone, he said.¹²

The other approach for patients truly refractory to lenalidomide is an IMiD-free regimen that incorporates drug classes that the patient has previously not had. The addition of a monoclonal antibody to carfilzomib/dexamethasone significantly improved PFS in the CANDOR trial of daratumumab (HR, 0.63; $P=.0014$)¹³ and in the recent IKEMA trial of isatuximab (HR, 0.531; $P=.0007$).¹⁴

New Drugs for Penta-Refractory Disease

Patients are increasingly exhausting all 3 main classes of drugs, “and for these patients, we have to start looking at new drug classes,” he said. One such drug, approved a year ago, is selinexor, an oral nuclear transport protein inhibitor that was shown to be effective in highly pretreated patients in the STORM trial.¹⁵ Subsequently, the phase III BOSTON study administered selinexor + Vd, with patients achieving a median PFS of approximately 14 versus 9 months with Vd alone (HR, 0.70; $P=.0075$).¹⁶ “This is a triplet we can utilize in patients who are highly refractory or in whom we don’t want to use a monoclonal antibody or IMiD,” he said.

The antibody–drug conjugate targeting B-cell maturation antigen, belantamab mafodotin, is another new drug that has been shown to be effective as a single agent in the single-arm registrational DREAMM2 trial.¹⁷ Patients derived benefit irrespective of prior drug exposure, including penta-refractoriness.

“Many of these new drug approvals and phase III data are incorporated into the updated NCCN Guidelines,” Dr. Kumar said. For previously treated patients, there are now 7 regimens that have category 1 recommendations, and a host of other recommended treatments that now include belantamab and selinexor. “This is clearly a long list of drugs and combinations, and it speaks to the progress that has been made in the field,” he concluded.

Disclosures: Dr. Kumar has disclosed receiving grant/research support from AbbVie, Inc., Amgen Inc., Bristol-Myers Squibb Company, CARsgen Therapeutics, Ltd., Celgene Corporation, Janssen Pharmaceutica Products, LP, Kite Pharma, MedImmune Inc., Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Roche Laboratories, Inc., sanofi-aventis U.S., Takeda Pharmaceuticals North America, Inc., and TeneoBio;

serving as a scientific advisor for AbbVie, Inc., Amgen Inc., Celgene Corporation, Genentech, Inc., Janssen Pharmaceutica Products, LP, MedImmune Inc., sanofi-aventis U.S., and Takeda Pharmaceuticals North America, Inc.; receiving honoraria from BeiGene; and receiving

consulting fees from Collectar Biosciences, Inc., GeneCentrix, Inc., and Oncopeptides.

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