Maneuvering the Complex Web of Treatment Options for Relapsed/Refractory Multiple Myeloma

Presented by Natalie S. Callander, MD

ABSTRACT

Numerous treatment options are available for patients with early relapsed multiple myeloma. Clinicians should consider using a monoclonal antibody for patients who have not yet received one, or changing either the immunomodulatory drug, the proteasome inhibitor, or both. Clinical trials are another option, or clinicians can refer transplant-naïve patients for autologous stem cell transplantation (ASCT). For patients with late relapse, a clinical trial is recommended, if possible, but many patients are ineligible due to poor blood cell counts or other factors. Additional treatment options include selinexor combinations, belantamab mafodotin-blmf, melphafen, or CAR T-cell therapy. Salvage ASCT should also be considered for this challenging population.

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As new drugs continue to be approved for the treatment of multiple myeloma (MM) at a rapid pace, there have never been more treatment choices available for patients with relapsed disease. Except for those with the highest-risk disease or plasma cell leukemia, most patients can expect initial disease control of at least 3 to 5 years, said Natalie S. Callander, MD, Professor of Medicine, University of Wisconsin Carbone Cancer Center. However, relapse is still inevitable for most patients.

At the NCCN 2021 Virtual Congress: Hematologic Malignancies, Dr. Callander discussed appropriate evaluation of patients with relapsed MM, as well as treatment of both early and late relapse, and several novel agents in development.

MM Treatment Paradigm

Most transplant-eligible patients will receive a triplet combination using a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an antibody drug followed by autologous stem cell transplantation (ASCT) and then maintenance therapy. Transplant-ineligible patients, alternately, will typically receive a triplet combination (often bortezomib/lenalidomide/dexamethasone or daratumumab/lenalidomide/dexamethasone).

“Based on published data, we anticipate that these patients will be stable for a very long time on continuous therapy,” said Dr. Callander. “However, with rare exceptions, all patients with MM experience relapse, and these relapses become increasingly difficult to treat over time.”

Defining Relapse

With respect to relapsed disease, Dr. Callander described 2 groups of patients requiring different interventions: those who experience disease progression defined by laboratory parameters (ie, biochemical disease progression) and those who experience disease progression defined by a new event (ie, systemic disease progression). Biochemical disease progression is currently defined by the International Myeloma Working Group as the reemergence of serum monoclonal (M) protein levels >0.5 mg/dL, urine M protein >200 mg/24 hours, and/or involved light chain level >10 mg/dL (100 mg/L). Some experts believe that patients with any increase in monoclonal proteins should be classified as relapsing and receive alternative therapy.

Conversely, symptomatic disease progression is defined the reemergence of anemia, renal insufficiency, or hypercalcemia; a new bone lesion or fracture; or a new extra medullary deposit. Clinicians may consider delaying treatment for patients with biochemical disease progression, said Dr. Callander, but those with symptomatic disease progression often require immediate therapy and quick decision-making.

Treatment of Early Relapse

For patients who experience relapse after 1 to 3 types of treatment, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MM strongly recommend introduction of a monoclonal antibody.¹ “For patients who have just biochemical progression, it might be reasonable to start with a doublet regimen, particularly if the

patient is frail and has responsive disease,” said Dr. Callander. “However, triplets tend to beat doublets in almost every trial.”

The triplets discussed in the following sections have been FDA-approved for use in this patient population.

Daratumumab/Pomalidomide/Dexamethasone

One of the most frequently selected regimens for first relapse and the most widely used in the United States is subcutaneous daratumumab/pomalidomide/dexamethasone. At a median follow-up of 16.9 months, data from the phase III APOLLO trial showed a median progression-free survival (PFS) of 12.4 months with the triplet regimen versus 6.9 months with the doublet pomalidomide/dexamethasone alone (hazard ratio, 0.63).² The overall response rate (ORR) for the triplet combination was 69% versus 46% for the doublet.

Daratumumab/Carfilzomib/Dexamethasone

Daratumumab/carfilzomib/dexamethasone was approved based on results of the CANDOR trial,³ which randomly assigned patients to that triplet combination versus carfilzomib/dexamethasone. The phase III study showed very good responses for both arms, said Dr. Callander, but median PFS has not been reached with daratumumab/carfilzomib/dexamethasone versus 15.8 months with carfilzomib/dexamethasone. The ORR was 84% in the investigational arm versus 75% with the doublet, both of which are quite high.

Isatuximab/Carfilzomib/Dexamethasone

Data from the IKEMA trial showed an ORR of 87% in patients with early relapse who received isatuximab/carfilzomib/dexamethasone versus 83% with carfilzomib/dexamethasone.⁴ Although not a significant difference in the response rate, Dr. Callander said, the quality of responses favored the isatuximab arm, with investigators demonstrating a doubling of measurable residual disease (MRD) negativity in those receiving the triplet combination. “We think this kind of marker may translate to better control for a longer period for this group of patients,” Dr. Callander said.

Elotuzumab/Pomalidomide/Dexamethasone

The combination of elotuzumab/pomalidomide/dexamethasone has outperformed pomalidomide/dexamethasone, with a median PFS of 10.3 versus 4.7 months, respectively.⁵ Dr. Callander also noted “flattening of the curve” in patients who received the triplet regimen. “Elotuzumab tends to be better tolerated than other anti-CD38 antibodies, so this is a very reasonable choice to consider in patients as well,” Dr. Callander said.

Early Relapse With Prior Antibody Therapy

For patients with early relapsed MM whose disease is refractory to monoclonal antibody therapy, Dr. Callander

recommended changing either the PI, the IMiD, or both. Using an oral triplet regimen is another consideration during the COVID-19 pandemic in order to limit in-person visits. There are phase III data supporting the combination of ixazomib/lenalidomide/dexamethasone, said Dr. Callander, but there are other approved combinations (ClinicalTrials.gov identifier: NCT02343042). The combination selinexor/pomalidomide/dexamethasone, for example, would offer a patient a different mechanism of action in this situation, she added.

Treatment of Patients With Late Relapse

According to Dr. Callander, patients who experience late relapse (after >3 prior therapies) are the most challenging to treat. The fitness and stability of patients become increasingly important to assess, she said, and emphasized that clinicians should always seek if a clinical trial is available. If the patient has never undergone transplantation, and cells are available, clinicians should strongly consider ASCT or the addition of alkylator therapy. For patients with triple-class refractory disease (ie, no longer responsive to a PI, IMiD, or monoclonal antibody) survival is often poor and typically measured in months. “This group of patients is quite tough to treat,” said Dr. Callander. “We are hoping to come up with better strategies for them.”

The following sections discuss some options for this patient population.

Selinexor

Selinexor, an XPO1 inhibitor which is also approved for treatment of lymphoma, is available for patients with heavily pretreated MM. Results of the STORM trial, which combined selinexor twice weekly with dexamethasone in patients who were heavily pretreated (an average of 7 lines of therapy), showed an ORR of approximately 26%, with a minimal response of approximately 40%.⁶

“Selinexor is a very useful drug, but it is not very well tolerated in twice-weekly dosing,” said Dr. Callander, who noted that a more appropriate dose is approximately 60 to 80 mg weekly. “Using aggressive prophylaxis with antiemetics is also important.” Furthermore, according to Dr. Callander, selinexor combinations (with lenalidomide, pomalidomide, carfilzomib, or daratumumab) look promising.

Belantamab Mafodotin-blmf

An off-the-shelf anti-B-cell maturation antigen (BCMA) therapy, belantamab mafodotin-blmf, is the first antibody-drug conjugate to be approved by the FDA for the treatment of MM. Results of the DREAMM-2 study showed an ORR of 31%, said Dr. Callander, including some patients with “extraordinarily prolonged response.”⁷

According to Dr. Callander, the most irksome adverse effect of belantamab mafodotin is keratopathy,

which clinically manifests as irritated eyes, dry eyes, or blurry vision. Routine evaluation by an ophthalmologist or optometrist is required to monitor for the development of keratopathy and to determine whether a dose hold is indicated. Additionally, combinations with belantamab mafodotin are also coming soon, she stated, noting that data with both pomalidomide and bortezomib look “quite promising.”

Melphalan Flufenamide

Flufenamide is the first aminopeptidase-targeted peptide-drug conjugate. In the pivotal phase II HORIZON study, the activity of melphalan + dexamethasone was demonstrated in heavily pretreated patients with relapsed/refractory MM who were refractory to pomalidomide and/or anti-CD38 monoclonal antibody therapy, with acceptable safety.⁸ Data from the study demonstrated an ORR of 29%, with a median PFS of 4.2 months, and a median overall survival of 11.6 months. Grade 3/4 hematologic adverse events were common (neutropenia [79%], thrombocytopenia [76%], and anemia [71%]), but were clinically manageable. Nonhematologic adverse events were infrequent.

“This drug is given once a month, which is convenient,” said Dr. Callander, who noted that combination testing is currently on hold due to FDA concerns regarding toxicity, although the drug remains available at this time.

CAR T-Cell Therapy

The first CAR T-cell therapy for MM, idecabtagene vicleucel, was approved in March 2021. Results of the KarMMa study, which examined the anti-BCMA CAR T-cell product, showed an impressive ORR, which appeared to be

correlated with the number of cells infused.⁹ The highest percentage of response was observed in patients who received the highest dose levels. The median overall PFS was 10.3 months, with an overall survival of 34 months, and the duration of response was up to 22 months for patients who achieved a complete response. “One of the most gratifying things about CAR T-cell therapy is the speed of the responses,” said Dr. Callander, who noted that responses typically occur within 1 month.

Although cytokine-release syndrome was a common toxicity (84%), its severity was limited in most participants. “Patients typically develop a fever, chills, or changes in blood pressure within 24 hours of receiving idecabtagene vicleucel, but most are responsive to tocilizumab or steroids,” said Dr. Callander, who noted that the frequency and intensity of neurotoxicity were also low. “Only a few patients developed grade 3 neurotoxicity requiring intervention.”

Idecabtagene vicleucel is indicated for patients with MM who have received >4 lines of therapy, including a PI, an IMiD, and an anti-CD38 antibody. In addition to manufacturing time, Dr. Callander noted the accessibility to CAR T-cell therapy as a limitation. “There are only about 70 sites in the United States that are currently allowed to offer CAR T-cell therapy, so this can really be an issue for an unstable patient, who requires immediate therapy and may not be able to wait for cell manufacturing” she said.

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

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