Evolution of Therapy for Relapsed/Refractory Multiple Myeloma

Presented by Jorge J. Castillo, MD

ABSTRACT

With so many recent advances in relapsed/refractory multiple myeloma, keeping abreast with current treatment recommendations can be challenging. Novel immunomodulators, proteasome inhibitors, monoclonal antibodies, histone deacetylase inhibitors, and nuclear export inhibitors have all been added to the armamentarium, and the choice of which of these drugs or drug combinations to use depends on individual disease-related and patient-related factors, previous therapies, and treatment toxicities. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Dr. Jorge J. Castillo provided an overview of the myriad treatments available for patients with relapsed/refractory multiple myeloma, as well as therapies on the horizon.

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Numerous advances have recently been made in the treatment of relapsed/refractory (R/R) multiple myeloma (MM): novel immunomodulators, proteasome inhibitors, monoclonal antibodies, histone deacetylase inhibitors, and nuclear export inhibitors have all been added to the armamentarium. According to Jorge J. Castillo, MD, Associate Professor, Harvard Medical School and Dana-Farber Cancer Institute, keeping up with these advances can be incredibly challenging for providers. “I would say myeloma is an area of oncology in which a higher variety of medications have been approved in recent years than in any other oncology malignancy,” he said. “And that’s, in itself, a good thing. But then it also gives us a number of headaches.”

According to Dr. Castillo, the main headache is the sheer number of treatment options outlined in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MM (Figure 1). At the NCCN 2019 Annual Congress: Hematologic Malignancies, Dr. Castillo provided recommendations for navigating these complex treatment scenarios in R/R MM.

Factors to Consider for Treatment Selection

“You could basically create a wheel of fortune. The patient comes in, you say, ‘spin,’ and wherever the wheel stops is the treatment you provide,” he quipped. “But that’s not a scientific way to treat patients with MM.”

According to Dr. Castillo, treatment selection comes down to personalization. When selecting treatment for patients with R/R MM, providers should keep in mind certain disease-related factors, such as the nature of relapse (indolent vs aggressive), risk stratification (high,

intermediate, or low), genomic abnormalities, and disease burden. “If the patient relapses with localized disease versus a more generalized relapse, that can give us an idea of how we should choose different treatments,” he noted.

A number of patient-related factors also contribute to treatment selection. For example, 40% to 50% of patients with MM will have some degree of renal insufficiency. For these patients, medications that are more likely to provide efficacy with lower toxicity, such as cyclophosphamide, proteasome inhibitors, and dose-reduced immunomodulatory drugs (IMiDs), should be favored. “At least in the R/R setting, patient preference has become much more important,” he noted. Convenience (ie, preference for oral vs intravenous therapy), distance required to travel for treatment, out-of-pocket costs, and insurance coverage should all be carefully weighed.

Previous therapy is one of the most important aspects to consider, he added. For example, did the patient’s disease progress while receiving proteasome inhibitors or IMiDs? Did it progress on or off maintenance? What was the depth and duration of response? The answers to these questions should inform treatment decisions.

Finally, there is the issue of treatment toxicity. In general terms, Dr. Castillo advised minimizing exposure to bortezomib and thalidomide in patients with pre-existing neuropathy, and recommended caution using carfilzomib in patients with cardiac issues and elderly patients, daratumumab in those with pulmonary issues, and IMiDs in patients with prior thrombotic episodes.

<div> <div> National Comprehensive Cancer Network® </div> </div> <div> NCCN Guidelines Version 1.2020 Multiple Myeloma </div>	
MYELOMA THERAPY^{a-c,f,g,i,j,r,s} THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA^t	
Preferred Regimens <ul style="list-style-type: none"> • Bortezomib/lenalidomide/dexamethasone • Carfilzomib (twice weekly)/dexamethasone (category 1)^k • Carfilzomib (weekly)/dexamethasone^k • Carfilzomib/lenalidomide/dexamethasone (category 1)^t 	<ul style="list-style-type: none"> • Daratumumab^p/bortezomib/dexamethasone (category 1) • Daratumumab^p/lenalidomide/dexamethasone (category 1) • Elotuzumab^w/lenalidomide/dexamethasone (category 1)^t • Ixazomib/lenalidomide/dexamethasone (category 1)^t
Other Recommended Regimens <ul style="list-style-type: none"> • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Bortezomib/dexamethasone (category 1)^k • Daratumumab^{p,u} • Daratumumab^p/carfilzomib/dexamethasone • Daratumumab^p/pomalidomide^v/dexamethasone • Elotuzumab/bortezomib/dexamethasone 	<ul style="list-style-type: none"> • Elotuzumab/pomalidomide/dexamethasone^v • Ixazomib/cyclophosphamide/dexamethasone • Ixazomib/dexamethasone^k • Ixazomib/pomalidomide/dexamethasone • Lenalidomide/dexamethasone^v (category 1)^k • Panobinostat^z/bortezomib/dexamethasone (category 1) • Panobinostat^z/carfilzomib^k • Panobinostat^z/lenalidomide/dexamethasone • Pomalidomide^x/cyclophosphamide/dexamethasone • Pomalidomide^x/dexamethasone^v (category 1)^k • Pomalidomide^x/bortezomib/dexamethasone (category 1) • Pomalidomide^x/carfilzomib/dexamethasone
Useful in Certain Circumstances <ul style="list-style-type: none"> • Bendamustine • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)^m 	<ul style="list-style-type: none"> • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)^m ± bortezomib (VTD-PACE)^m • High-dose cyclophosphamide • Selinexor/dexamethasone^{aa}

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Figure 1. Therapy options for those who received prior therapy for multiple myeloma.

From the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma. Version 1.2020. To view the most recent version, visit NCCN.org.

He noted that although these drugs are not actually contraindicated, following some general rules of thumb can help narrow down the treatment options. “Every intervention that we have will result in some toxicity,” he said. “We need to make sure that the benefit we provide to our patients is higher than the potential toxicity.”

Early Relapse: Lenalidomide/Dexamethasone

Adding carfilzomib to a lenalidomide/dexamethasone regimen (KRD) has shown promising efficacy in patients with MM after first relapse, as evidenced in a study by Stewart et al.¹ With approximately 400 patients in each arm, patients in the carfilzomib arm had superior progression-free survival (PFS) compared with those in the lenalidomide/dexamethasone arm (median, 26.3 vs 17.6 months). However, Dr. Castillo pointed out that only 20% of study patients had been previously exposed to lenalidomide. “So how applicable would this be in a world in which all of our patients have been previously exposed to lenalidomide?” he questioned.

Another option involves adding ixazomib, an oral proteasome inhibitor, to lenalidomide/dexamethasone in the R/R setting. Investigators from France compared this triplet regimen and observed a superior PFS of 20.6 versus 14.7 months, respectively.² Prior lenalidomide exposure in this study (~360 patients in each arm) was approximately 12%.

Daratumumab added to lenalidomide/dexamethasone has shown similar efficacy. In a European trial of 569 patients, 18% of which had prior lenalidomide exposure, median PFS was not reached in the daratumumab arm compared with 17.5 months in the lenalidomide/dexamethasone arm.³

Furthermore, elotuzumab, when added to lenalidomide/dexamethasone in patients with minimal prior lenalidomide exposure (6%), resulted in similar improvements in PFS of approximately 19, versus 15 months without elotuzumab.⁴ Unlike daratumumab, elotuzumab has not demonstrated notable efficacy as a single agent, he noted.

However, Dr. Castillo warned that, “despite how good these numbers look, the applicability is limited,” because most patients in clinical practice will have had higher exposure to lenalidomide.

Early Relapse: Bortezomib/Dexamethasone

In a study of almost 1,000 patients with R/R MM with nearly 40% prior exposure to lenalidomide, carfilzomib added to dexamethasone led to a “remarkable” PFS benefit compared with bortezomib/dexamethasone.⁵ A sister study showed that the addition of daratumumab to bortezomib/dexamethasone in patients with 68% prior exposure to lenalidomide was superior to the control group receiving only bortezomib/dexamethasone.⁶ “All of these studies really show us that triplets are the way to

go, not only for frontline disease but also for relapsed disease,” he said.

Dr. Castillo noted that neuropathy tends to be more problematic in patients on proteasome inhibitors. Although infections are more common with daratumumab combinations, cardiotoxicity is more prominent with the use of carfilzomib, and diarrhea occurs across the board. Being aware of these toxicity trends can help guide treatment, he said (Table 1).

Late Relapses (Second Relapse and Later)

“This is where pomalidomide-based regimens are an important resource,” he said. In the recently published phase III OPTIMISMM trial,⁷ adding pomalidomide to bortezomib/dexamethasone resulted in superior PFS in patients previously treated with lenalidomide. Dr. Castillo noted that this regimen is “reasonable” in this scenario, but it is important to remain vigilant about the risk of neuropathy.

Elotuzumab + pomalidomide/dexamethasone has also shown significant benefit in this setting.⁸ Dr. Castillo maintained that this combination is highly desirable for patients after second relapse who had previous exposure to daratumumab. However, he noted that the effect of elotuzumab after treatment failure or disease progression on daratumumab is still unknown; but the opposite is also true in regard to the effect of daratumumab after treatment failure on elotuzumab. “I think in most academic centers we feel that daratumumab is a more potent antibody than elotuzumab, and maybe daratumumab failures will be elotuzumab failures,” he said. “But we don’t have data to actually support that at this time.”

In a single-arm study, combination daratumumab/pomalidomide/dexamethasone showed promise in heavily pretreated patients with R/R disease not previously

exposed to daratumumab or pomalidomide.⁹ Additionally, in a study by Rosenbaum et al,¹⁰ carfilzomib/pomalidomide/dexamethasone demonstrated favorable outcomes, with most lenalidomide-refractory patients achieving a major response. Some data have suggested efficacy with panobinostat-based regimens in this patient population when combined with dexamethasone/bortezomib.¹¹

Primary Refractory Disease

Clinical trials have not yet been designed specifically for patients with primary refractory MM. “We treat [these] patients with what we already have, but we don’t have clinical data supporting specific approaches in this type of patient, besides getting them to transplantation early and using a triplet or even a quadruplet as data accumulate,” he said.

Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) should be standard in transplantation-eligible patients who experienced relapse after primary therapy that did not include ASCT, and a second ASCT should be considered for patients whose disease relapsed after primary therapy that did include ASCT (with initial remission >18 months).

Allogeneic stem cell transplantation can be considered in patients with high-risk disease who experience early relapse (<24 months) after primary therapy that included ASCT.¹² He noted that this specific recommendation should be strongly encouraged in the context of clinical trials.

Final Recommendations

Dr. Castillo urged consideration of a non-lenalidomide triplet in patients whose disease progressed on lenalidomide maintenance, and a lenalidomide-based triplet

Table 1. Selected Grade ≥3 Adverse Events of New Combinations in Patients With Relapsed/Refractory Disease

	Proteasome Inhibitors			Monoclonal Antibodies			Immunomodulators	
	ENDEAVOR (Kd)	ASPIRE (KRd)	TOURMALINE (IRd)	POLLUX (DRd)	CASTOR (DVd)	ELOQUENT-2 (EloRd)	OPTIMISMM (PVd)	ELOQUENT-3 (EloPd)
Neuropathy	2%	3%	2%	NR	5%	NR	9%	NR
Renal	3%	3%	3%	NR	NR	NR	NR	0%
Cardiac	5%	7%	3%	NR	NR	NR	NR	7%
Infections	6%	2%	<1%	9%	10%	NR	9%	13%
Diarrhea	3%	4%	6%	5%	4%	5%	7%	0%
Fatigue	5%	8%	4%	6%	5%	8%	8%	0%
Rash	NR	NR	5%	NR	NR	NR	NR	0%

Abbreviations: DRd, daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EloPd, elotuzumab/pomalidomide/dexamethasone; EloRd, elotuzumab/lenalidomide/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; NR, not reported; PVd: pomalidomide, bortezomib, dexamethasone.

in those who experienced a prolonged treatment-free survival after lenalidomide-based induction. But he also advised consideration of a triplet regimen with different novel agents in patients with primary refractory MM, and to always consider referring for transplantation if no ASCT was performed during induction.

CAR T-cell therapies, antibody–drug conjugates, and bispecific T-cell engagers against B-cell maturation antigen and other targets are currently under development

for the treatment of R/R MM, and these up-and-coming treatments should be on oncologists' radar.

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