Individualizing Care for Multiple Myeloma: Navigating Treatment Options and Addressing Patient Needs

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Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2024.15.3.10

Abstract

At JADPRO Live 2023 in Orlando, presenters discussed selecting treatment regimens for newly diagnosed and relapsed or refractory multiple myeloma. They also provided insights on comprehensive care centered around patient preferences, treatment goals, side effect mitigation, and supportive care needs of patients with multiple myeloma.

There have been enormous improvements in the treatment of patients with multiple myeloma (MM), leading to patients living longer with the disease. At JADPRO Live 2023, Beth Finley-Oliver, MSN, ARNP, AGNP-BC, a nurse practitioner in the department of Malignant Hematology at Moffitt Cancer Center, and Rachid Baz, MD, Multiple Myeloma Section Head in the Department of Malignant Hematology at Moffitt Cancer Center, covered managing newly diagnosed, early relapsed, and advanced MM, as well as the role, sequence, and adverse events of anti-CD38 monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapies, and bispecific T-cell engager (BiTE) therapies.

NEWLY DIAGNOSED MM

The SWOG S0777 study examined induction therapy in previously untreated patients without an intent for immediate autologous stem cell transplant. It compared bortezomib, lenalidomide, and dexamethasone (VRd) with lenalidomide and dexamethasone (Rd). Adding bortezomib for 6 months resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS; 41 months for VRd vs. 29 months for Rd) as well as overall survival (OS; not reached for VRd vs. 69 months for Rd with a hazard ratio [HR] of 0.71). In the subgroup analysis, improvement was seen irrespective of age. A smaller phase II trial evaluated modified lenalidomide, bortezomib, and dexamethasone (VRd-lite) in transplant-ineligible MM patients that showed "a very robust response rate." This could be a consideration for frailer older adults.

The MAIA study looked at another 3-drug regimen, adding a

J Adv Pract Oncol 2024;15(3):204–208

monoclonal antibody that targets CD38. Daratumumab plus lenalidomide and dexamethasone (Dara-Rd) increased OS and PFS over Rd in patients ineligible for stem cell transplant with newly diagnosed MM. Median PFS was not reached in the daratumumab group vs. 34.4 months in the control group.

"The main message is you can't compare across studies, because in one case we continued daratumumab until progression along with lenalidomide, and in the other one we gave just 6 months of added bortezomib that translated into a survival benefit of about a year," commented Dr. Baz.

The ENDURANCE trial compared two induction regimens, carfilzomib, lenalidomide, and dexamethasone (KRd) vs. VRd and showed that there was not a significant difference between the two proteasome inhibitors (carfilzomib or bortezomib) in combination with lenalidomide and dexamethasone for patients with newly diagnosed MM without high risk features (except for t[4;14]). However, the bortezomib arm was associated with a greater risk of neuropathy whereas the carfilzomib arm resulted in greater cardiovascular adverse events. According to the presenters, this allows for the personalization of therapy based on which adverse event is most important to avoid for a specific patient.

"We often hear with carfilzomib that there's cardiac toxicity. In my experience, it is more often hypertension that we see with carfilzomib, with other, more serious cardiac events being uncommon," commented Ms. Finley-Oliver.

The GRIFFIN study evaluated the addition of daratumumab to VRd (D-RVd arm) followed by transplant, consolidation, and maintenance lenalidomide in transplant-eligible newly diagnosed MM patients. There was a deeper response in those patients receiving D-RVd, with improved rates of durable minimal residual disease (MRD) negativity compared with RVd. There was a positive trend toward improved PFS for D-RVd/DR vs. RVd/R; however, the separation of the PFS curves begins beyond 1 year, and it remains unclear if the benefit is due to the addition of daratumumab during induction or maintenance.

Looking at another anti-CD38 monoclonal antibody, isatuximab in addition to lenalidomide, bortezomib, and dexamethasone produced a higher overall response rate compared with RVd (50% and 36%, respectively).

"With CD38 monoclonal antibodies, you have to worry about infection risk. If a patient has hypogammaglobulinemia, don't be afraid to use intravenous immunoglobulin (IVIG)," added Ms. Finley-Oliver.

In the MASTER trial, newly diagnosed myeloma patients received daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) induction therapy, autologous hematopoietic cell transplant (AHCT), and Dara-KRd consolidation. It was an MRD-driven trial that used next-generation sequencing (NGS) to inform the use and duration of therapy. Patients with two MRD-negative tests were able to discontinue therapy. This study showed a high rate of MRD negativity in newly diagnosed MM; however, patients who had two or more high-risk cytogenetic abnormalities experienced early progression after discontinuation of therapy. In addition, the PFS rates of these high-risk patients in the MASTER and GRIFFIN daratumumab-based quadruplets were similar and inadequate, signaling the need for better treatment options for these patients.

Role of Transplant

The DETERMINATION trial examined patients with newly diagnosed MM treated with VRd with and without an autologous stem cell transplant (ASCT). All patients received lenalidomide maintenance until progression. Patients with ASCT experienced significantly longer median PFS (67.5 months) compared with those without ASCT (46.2 months). The 5-year overall survival was similar between the two arms (HR 1.10), with patients who were MRD positive having a better outcome from transplant.

"The decision to proceed with transplant is an individual discussion with patients about their goals," commented Ms. Finley Oliver. "But I think there will come a time when the choice is informed by risk and response."

Does consolidation therapy matter? The STaMINA trial compared AHCT, tandem AHCT, and AHCT and four subsequent cycles of lenalidomide, bortezomib, and dexamethasone (RVd; AHCT + RVd), all followed by lenalidomide until

disease progression. Results showed that a second AHCT or RVd consolidation did not improve PFS or OS.

"Therefore, there is really no advantage to tandems or consolidation therapy," concluded Dr. Baz.

To summarize, for frail or old patients, Dara-Rd is recommended for most newly diagnosed MM patients as it is likely to result in fewer adverse events than VRd. VRd-lite can be considered for patients with t(4;14) until best response and then lenalidomide and bortezomib maintenance. If patients have renal failure, Dara-Vd can be considered, along with the consideration for adding cyclophosphamide for one to two cycles. Patients can be switched to lenalidomide maintenance if their renal function resolves or improves.

For the young and fit patients, VRd can be considered if there is no history of peripheral neuropathy, along with the addition of daratumumab based on the GRIFFIN and PERSEUS trial. KRd is an option if there is a history of peripheral neuropathy but no cardiovascular issues. Clinicians can plan for ASCT in best response (4 to 8 cycles) ideally in very good partial response or better. Dara-VCd is an option if there is renal failure at presentation, with a change to Dara-RVd when renal function resolves or improves.

ADVERSE EVENTS

Common side effects seen with immunomodulatory drugs (IMiDs) are myelosuppression, fatigue, and diarrhea.

"If patients have had a great response and they have myelosuppression, it makes sense to hold therapy. Other options include growth factors, antibiotics, and IVIG if needed," commented Ms. Finley-Oliver.

Fatigue is common across the board with MM therapies. Physical therapy and exercise are recommended to mitigate it.

A rash can occur with IMiDs, usually in the first few cycles.

"I like to use oral antihistamines for the rashes, especially for lenalidomide. If the rash is severe, you should stop therapy and administer steroids," said Ms. Finley-Oliver.

Thromboembolic events have been reported with IMiDs.

"If patients have a history of deep vein thrombosis or if they're sedentary, it makes sense to recommend anticoagulation. If there is no history, a baby aspirin works well for the prevention of clots," said Ms. Finley-Oliver.

Gastrointestinal adverse events such as intermittent loose stools are common with both IMiDs and proteasome inhibitors (PIs).

"For many patients, I put them on fiber immediately. There are also bile acid binding resin medications. Cholestyramine works beautifully for this type of diarrhea," commented Ms. Finley-Oliver.

Bispecific antibodies and CAR T-cell therapy carry the risk for cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS).

Infusion reactions are seen with monoclonal antibodies and usually during the first one or two doses, but it is not common. Patients can usually be pulled off of premedications quickly.

For neuropathy, caution should be taken around using bortezomib, with dose reductions when appropriate.

"The biggest key is focusing on prevention," said Ms. Finley-Oliver.

EARLY RELAPSED DISEASE

The most common situation for MM patients is relapsing during lenalidomide maintenance. The CANDOR study compared carfilzomib, dexamethasone, and daratumumab (KdD) vs. carfilzomib and dexamethasone (Kd) in adults with relapsed/refectory MM with one to three prior therapies. The final analysis of CANDOR confirmed that the addition of daratumumab improved outcomes and did not add significantly in terms of toxicity. The IKEMA study showed that the same outcomes can be achieved with the other anti-CD38 monoclonal antibody, with isatuximab, carfilzomib, and dexamethasone.

The APOLLO study looked at daratumumab plus pomalidomide and dexamethasone, which reduced the risk of disease progression or death vs. pomalidomide and dexamethasone alone and could be considered a treatment option in this setting.

The addition of isatuximab to pomalidomide and dexamethasone in the ICARIA study significantly improved PFS in patients refractory to lenalidomide and a proteasome inhibitor.

"The appeal of these pomalidomide-based regimens vs. CD38-K is that pomalidomide is more portable and so it's convenient for patients," added Dr. Baz.

Venetoclax, an oral BCL-2 inhibitor, has single-agent activity in patients with relapsed or refractory MM with t(11;14) translocation. In the global, randomized phase III CANOVA study, venetoclax plus dexamethasone (VenDex) demonstrated a numerically longer PFS compared with pomalidomide and dexamethasone (PomDex) in patients with t(11;14)-positive relapsed or refractory MM, although the difference was not statistically significant. The presenters, however, support the use of venetoclax for patients with t(11;14).

To summarize, for early relapsed patients, if the patient is lenalidomide naive or lenalidomide relapsed and CD38 monoclonal antibody naive, Dara-Rd or KRd can be considered (for patients with t[4;14], for example). If the patient is lenalidomide refractory and CD38 monoclonal antibody naive, either DaraPomDex or DaraKD can be considered. Isatuximab can be substituted for daratumumab. For patients who are lenalidomide refractory and CD38 monoclonal antibody refractory, combinations such as EloPomDex, KPomDex, or pomalidomide, cyclophosphamide, and dexamethasone can be considered. For lenalidomide naive or relapsed and CD38 monoclonal antibody refractory, EloRD or KRD is an option. Clinical trials should always be considered when available (see Figure 1 for a list of current MM drugs).

BCMA × CD3 BISPECIFICS

There is a crowded field of BCMA bispecifics in myeloma. Elranatamab and teclistamab have been FDA approved, and alnuctamab, linvoseltamab, and ABBV-383 are currently in development. They have similar response rate in patients who have advanced myeloma. For example, teclistamab had an overall response rate of 63%, with 70% of patients experiencing CRS.

The main toxicities are CRS and ICANS. Cytopenias are manageable and often transient. Hypogammaglobulinemia can be managed with IVIG.

The CAR T Consortium found that if a patient was given a BCMA bispecific antibody prior to CAR T-cell therapy, their outcome from CAR T-cell therapy was not as good. If patients received elranatamab or teclistamab after BCMA-directed therapy, including CAR T-cell therapy, the response rate was lower, at about 50%. Accordingly, the presenters recommended reserving BCMA-targeting bispecific therapies for patients who have received or are not eligible for BCMA CAR T-cell therapy.

Talquetamab, a GPRC5D × CD3 bispecific antibody, had response rates of around 60% to 70%. The main toxicity of talquetamab is CRS along with ICANS but was manageable. Another on-target effect of GPRC5D bispecific is dysgeusia

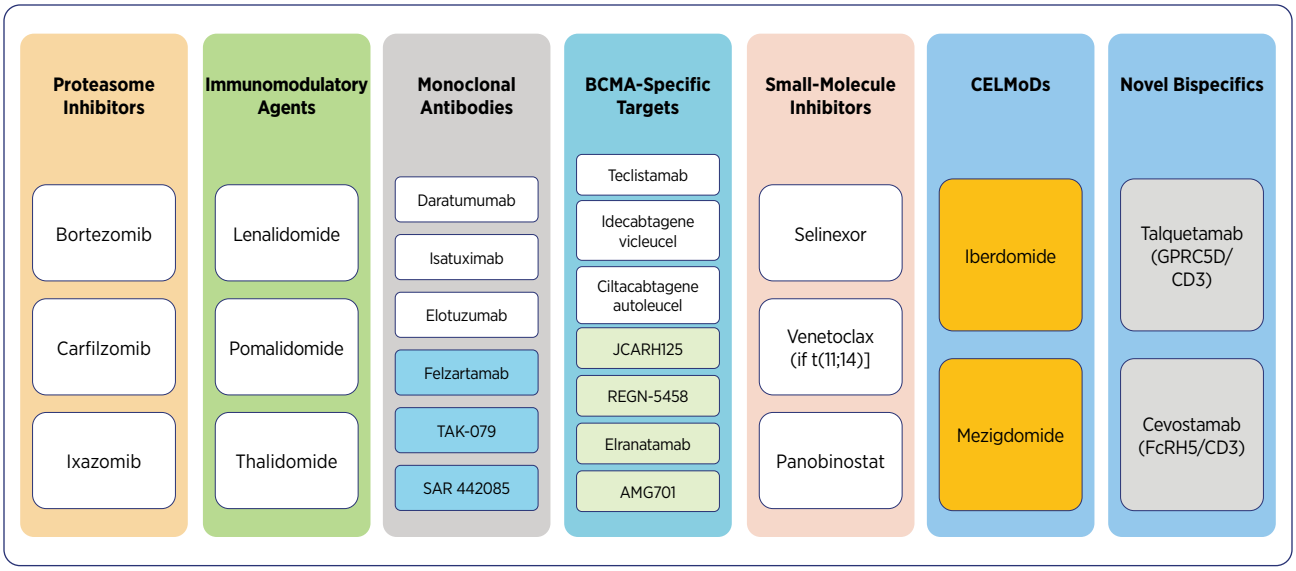

Figure 1. Navigating the MM drug arsenal.

and rashes because GPRC5D is also present on the taste buds and skin.

Cevostamab is another bispecific antibody targeting FcRH5 and CD3. It is still on trial and not approved but has very encouraging activity.

The two approved CAR T-cell products are idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), both of which are B-cell maturation antigen-directed CAR T-cell therapies. KarMMa-3 showed that ide-cel therapy significantly prolonged PFS and improved response as compared with standard regimens in patients with triple-class–exposed relapsed and refractory MM who had received two to four regimens previously. CARTITUDE-4 was a global, phase III, randomized, controlled trial of cilta-cel vs. standard of care (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]) in lenalidomide-refractory patients who had one to three prior lines. Cilta-cel was superior to these standard-of-care regimens in terms of MRD negativity and PFS.

In summary, there are a number of novel effective therapies for patients with multiple myeloma and many more on the horizon. ●

Disclosure

Dr. Baz has received research support from AbbVie, BMS, Janssen, Karyopharm, and Regeneron, has served on the advisory board for BMS, Janssen, and has received honoraria from HIKMA Cancer Network (CME presentation), GSK (member of response assessment committee). Ms. Finley-Oliver has no relevant financial relationships to disclose.