The rapid evolution and increasing complexity of multiple myeloma (MM) treatment over the past few years have improved patient outcomes and introduced challenges for practitioners and payers in determining the optimal therapy for a given patient. Key contributors to these challenges include both a lack of head-to-head randomized trials of commonly used triplet regimens and a patient population in real-world clinical settings that often does not reflect those of clinical trials. Therefore, real-world evidence (RWE) often is useful in identifying groups of patients likely to benefit from a given regimen. In a recent AJMC® Peer Exchange™, entitled, “Role of Real-World Evidence in the Evolving Treatment Landscape of Multiple Myeloma,” managed-care decision makers and experts in the treatment of MM discussed ways of using RWE to fill research gaps, improve delivery of effective and safe therapies, and reduce costs. The session was moderated by Ryan Haumschild, PharmD, MS, MBA, director of pharmacy services at Emory Healthcare and Winship Cancer Institute in Atlanta, Georgia.

EVOLVING MM TREATMENT LANDSCAPE

Although considered a single clinical entity, MM encompasses multiple cytogenetically distinct plasma cell malignancies that often undergo genomic changes over time; these transformations may be explained by clonal evolution or heterogeneity as well as mutations in individual genes.1,2 For this reason, combination therapies having different and complementary mechanisms to target coexisting disease may be beneficial, particularly for patients with high-risk or relapsed/refractory (RR) disease.2

The increased availability of new drugs and combination regimens and the inclusion of novel agents into initial treatment plans have led to improved overall survival (OS) in patients given a diagnosis of MM.1,3 In addition to alkylators and corticosteroids, therapies used for MM include immunomodulatory agents (IMiDs) (eg, lenalidomide, thalidomide, and pomalidomide); proteasome inhibitors (PIs) (eg, bortezomib, carfilzomib, and ixazomib); monoclonal antibodies against SLAMF7 (eg, elotuzumab) and CD38 (eg, daratumumab); and the histone deacetylase inhibitor panobinostat.3
Promising investigational therapies include chimeric antigen receptor (CAR) T-cell therapy that targets BCMA; further, GSK2857916 is a BCMA-targeting antibody conjugated to monomethyl auristatin-F, a microtubule-disrupting agent.1 The majority of patients with MM eventually relapse; the selection of treatment for RR MM depends on the timing of relapse, response to prior therapy, aggressiveness of disease at relapse, and performance status.7

The treatment costs for MM, particularly those for prescription drugs, are high. A retrospective cohort study of Medicare beneficiaries who entered the Surveillance, Epidemiology, and End Results registry from 2007 to 2015 showed that mean adjusted lifetime costs (2016 U$S using the Medical Care Component of the Consumer Price Index) were significantly higher in patients with MM ($234,002; 95% CI, $232,232-$235,870) than in matched patients without cancer ($49,507; 95% CI, $49,133-$49,903). Prescription drug costs contributed the most (44.9%) to incremental MM costs in the continuing care phase. The large contribution of prescription drug costs highlights the long-term use of expensive immunotherapy drugs given to prolong survival in MM; it also demonstrates a need for oncology care models to account for the dynamic nature of cancer management across the continuum of disease, particularly in relation to the use of novel agents.8

**Stakeholder Insights**

The rapid development of therapies has reshaped how patients with newly diagnosed and RR MM are treated; regimens effective in the RR setting are likely to be studied in increasingly earlier lines of treatment moving forward. “It’s fair to say that how we think of myeloma right now is not going to be the same [as] how we’re going to think about it within the next 5 years,” said Muhamed Baljević, MD, FACP, director of plasma cell disorders research and Vanderbilt amyloidosis programs at Vanderbilt University Medical Center in Nashville, Tennessee.

Although data are not available to confirm the superiority of 1 regimen over another, having more (3-4) novel agents with multiple mechanisms of action in a treatment regimen tends to lead to better outcomes due to the existence of subclones in MM, according to

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lems and ... capitalize [on] keeping those members on a longitudinal basis within our plan to really see the value that we brought.” Weaver added that matching therapies to the patients most likely to benefit from them is critical to optimally manage costs, which are often built out assuming an ideal response rate for a therapy—and clinical pathways could be used to standardize the experience. “What we see in trials is not what we see in the real world,” he said. “As we think about the real-world performance of these therapies, relative to that price point that was set on very idealistic adherence and outcomes, we know that there’s a gap, and so we need to bridge that gap.”

When considering the number of patients with MM and their lifespan, the costs of triplet regimens and related supportive care are astronomical, and real-world data (RWD) are needed to identify the optimal regimen for a given patient. “Myeloma [is] so complex, I don’t know that we’re ever going to have this as your 1 choice of front [line therapy]. This is your 1 choice in the relapse[d setting],” said Richter. “If we could get together enough data from [RWE and] clinical trial evidence and say [that] these several regimens up front are relatively equivalent, except 1 of them is significantly less [appropriate], then we can save here and, at the same time, provide top quality care to everyone.”

USE OF RWE IN MM

In addition to the complex and dynamic nature of MM, the lack of head-to-head trials comparing commonly used triplet regimens, differences in patient populations across trials of triplet regimens, and under-representation of patients of advanced age or with a high burden of comorbidities in randomized trials complicate selection of an optimal regimen for a patient with MM. Therefore, real-world comparative analyses have been initiated to bridge the gaps between clinical trial efficacy and RWE of common regimens used for MM.1

RWE and Clinical Practice Patterns With MM Triplet Regimens

To assess RWE of MM triplet regimens in relation to the corresponding efficacy of these regimens in clinical trials, a retrospective comparative analysis of time to next therapy (TTNT), used as a proxy for progression-free survival (PFS), was measured in a representative cohort of patients with RR MM from Optum’s deidentified electronic health record database; these patients were treated with IRd (ixazomib, lenalidomide [Revlimid], and dexamethasone), KRd (carfilzomib [Kyprolis], lenalidomide, and dexamethasone), or VRd (bortezomib [Velcade], lenalidomide, and dexamethasone) in line of therapy (LOT) 2 or greater after January 1, 2014. Real-world TTNT was also examined by frailty status (modified by age and comorbidities); patient, disease, and prior treatment characteristics independently associated with regimen selection were assessed.5

A total of 664 patients who initiated IRd, KRd, or VRd in LOT 2 or greater were identified; this accounted for 733 patient LOTs (IRd, 168 patients; KRd, 208 patients; VRd, 357 patients). Median age was significantly lower among the KRd group (65 years) than the IRd and VRd groups (71 years for both; P < .001).3 Significantly more patients given VRd (75.1%) were classified as intermediate/frail according to the modified frailty score than were those given IRd (67.3%) or KRd (69.7%) (P < .01). Treatment in LOT 2 was given to a greater proportion of patients in the VRd group (70.3%) than in the KRd (50.0%) and IRd groups (36.9%) (P < .001); fewer patients in the VRd group (13.7%) were refractory to a prior PI and/or IMiD than were those in the IRd (58.9%) and KRd (80.0%) groups (P < .001).3

The median duration of therapy was longer for patients given IRd (12.3 months) than for those given KRd (7.2 months) or VRd (10.0 months), and the risk of discontinuation of therapy was significantly lower with IRd than with KRd (HR, 0.71; 95% CI, 0.53-0.95; P < .0209). Risk for initiation of the next LOT or death was similar between patients receiving IRd and those given VRd (HR, 1.01; 95% CI, 0.78-1.30; P = .9562; median TTNT, 12.7 vs 14.2 months, respectively) and higher for those receiving KRd compared with patients treated with VRd (HR, 1.33; 95% CI, 1.07-1.66; P = .0112; median TTNT, 8.6 vs 14.2 months, respectively). Compared with those given KRd, patients initiating treatment with IRd had a lower risk for initiation of next LOT or death (HR, 0.76; 95% CI, 0.58-1.00; P = .0470). Multivariate subgroup analysis showed that among patients with a modified frailty score of intermediate to frail, the risk for initiation of next LOT or death was lower with IRd than with KRd (HR, 0.70; 95% CI, 0.49-0.98; P = .0389) and higher with KRd than with VRd (HR, 1.38; 95% CI, 1.00-1.89; P = .0481). However, TTNT was comparable among patients deemed to be fit according to the modified frailty score.3

The median TTNTs differed considerably from the PFS values in clinical trials of the corresponding treatment regimens.1 The phase 2 trial of VRd (NCT00378209) had a median PFS of 9.5 months, and patients had a median of 2 prior therapies (whereas 70% of the patients in the real-world study had 1 prior LOT).3 Although the phase 3 ASPIRE trial (NCT01080391) of KRd determined a median PFS of 26.3 months, the real-world TTNT for patients with 2 or more LOTs was 8.6 months.5 This may be due to larger proportions of patients in the real-world setting having high-risk cytogenetics (28% vs 13%) and prior exposure to an IMiD (73% vs 59%) when compared with those in the ASPIRE trial.1 The median PFS was also longer in the phase 3 TOURMALINE-MM1 study of IRd (NCT01564337) than was the corresponding median TTNT in the real-world study (20.6 months vs 12.7 months for LOT 2 or greater).3,5 This may be attributed in part to the higher proportion of patients in the real-world analysis receiving IRd in LOT 2 (60% vs 37%) and the lower proportion having prior IMiD exposure (54% vs 86%).5

If we could get together enough data from [RWE and] clinical trial evidence and say [that] these several regimens up front are relatively equivalent, except 1 of them is significantly less [appropriate], then we can save here and, at the same time, provide top quality care to everyone.

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COMPARING CLINICAL TRIAL EFFICACY WITH RWE

Analysis of RWD has also been used to assess how the efficacy and safety of an MM regimen in a real-world population compares with those observed among patients in a clinical trial. Approval of the IRd regimen for pretreated MM was based on results from the phase 3 TOURMALINE-MM1 study, which showed that the median PFS was longer in the group given IRd than in the group given placebo, lenalidomide, and dexamethasone (20.6 months vs 14.7 months, respectively; HR for disease progression or death, 0.74; 95% CI, 0.59-0.94; P = .01). The trial also showed that the PFS benefit was observed across all prespecified subgroups, including patients with high-risk cytogenetic abnormalities, those with International Staging System stage III disease, those aged older than 75 years, and those given 2 or 3 prior therapies. However, data are limited on outcomes with the IRd regimen in the real-world setting, which prompted researchers to conduct a multicenter, retrospective, observational study of patients with RR MM who received IRd via early access programs in Greece, the United Kingdom, and the Czech Republic. Among the 141 patients assessed for a response, the overall response rate (ORR) was 76.5% among patients given IRd as second-line therapy and 71.2% among those given IRd in the third line or higher. The median PFS was 27.6 months (95% CI, 15.1-29.8) for patients receiving IRd in the second line and 19.9 months (95% CI, 13.7-not estimable) for those receiving IRd in the third line therapy or higher. Compared with the TOURMALINE-MM1 trial participants, the patient population in this real-world study was slightly older and included more patients who had an Eastern Cooperative Oncology Group performance status greater than 1, at least 3 prior lines of therapy, and prior exposure to bortezomib, carfilzomib, and lenalidomide. However, the authors concluded that the ORR and median PFS were comparable to findings from the TOURMALINE-MM1 trial. These results, coupled with a limited toxicity profile that enables patients to receive long-term treatment, suggest that IRd can be used effectively and safely in a broad population of patients with MM.

Stakeholder Insights

Clinical trial populations tend to include patients treated at tertiary-care academic centers, whereas the majority of patients with MM in the real-world setting are treated at community hospitals and small health care settings. This discrepancy can lead to unintended biases in terms of patient selection and performance in clinical trials, according to Baljević. He also expressed concern that the median duration of therapy for many agents is shorter in the real-world setting than in clinical trials, which partially may be explained by many patients in the real-world setting not having support services to ensure receipt of necessary laboratory tests and reporting of symptoms that could be managed proactively. Baljević added that some of the historical comparator arms in the clinical trials are problematic, because they used suboptimal regimens in the control arm that would not be considered standard of care for the patient population studied (eg, comparing a doublet regimen with a triplet regimen in fit patients with RR MM).

The use of RWE for guiding treatment decisions is gaining momentum and is practically necessary for modifying therapeutic combinations. Richter cautioned that the quality of RWD needs to be considered when it is used to guide treatment decisions. He noted that while efficacy data are generally discrete and can be pulled retrospectively from RWD, adverse events are particularly difficult to capture in the real-world setting. Further, active development of prospective assessments of RWD is necessary for high-quality toxicity information.

In addition, RWE can provide more timely information to fill in gaps and support conclusions observed in clinical trials, which generally take much longer to generate results. “Everyone knew a particular regimen was superior, but it took 8 years to prove it in a randomized trial,” said Beveridge. “That doesn’t do anyone any good … The payers do really want to pay for the appropriate treatments. They just want to make sure from an actuarial standpoint that what they’re putting into their calculations and [what] they’re going to charge as premiums are valid.”

Baljević added that data modeling, RWE, and data pooling may have value in assessing the attrition rate with various therapies and comparing outcomes between 2 category 1–recommended regimens for which a head-to-head randomized trial has not been performed. Additionally, the increasingly longer PFS and OS in MM mean that randomized trial data take increasingly longer to obtain, and trials often shift to using surrogate end points, such as minimal residual disease status. “Running a study for many years costs millions of dollars. There’s [an] incredible amount of competing interest and [much] for us to learn [from a study],” said Baljević. Therefore, he said that drawing from RWE is important to avoid the large lag and catch-up inherent in producing data from randomized controlled trials.

Richter said that finding a “one-size-fits-all” treatment regimen is unlikely with MM, but RWE studies can determine ways, perhaps with a “multi-omic” approach that includes demographics, next-generation sequencing, immune profiles, proteomics, and metabolomics to identify therapies likely to be best for a particular subgroup of patients. He added that real-world studies could also help to address unmet needs, such as identifying patients who would benefit from DRd (daratumumab plus Rd) or VRd. Baljević said that incorporating quality-of-life data and other patient-reported outcomes would also be informative in situations in which regimens appear to have similar effectiveness and safety in the real world.

On the payer side, RWE is likely to play a role in the development of payer pathways for MM, because the complexity and costs of treatment for MM are substantially greater than are those for other cancers, according to Beveridge. However, he added that key opinion leaders (KOLs) need to play a role, because the credibility of the person making the treatment recommendations is an important factor influencing...
the wide uptake of this guidance among payers. Weaver said that although comparative data tend to be more helpful for pathway decision-making, noncomparative RWE can provide decision makers with additional data to support or contradict earlier policies or therapeutic selections for patients.

**FUTURE OF MM AND RWE—STAKEHOLDER INSIGHTS**

Richter stated that KOLs at major myeloma centers and the FDA need to continue to bring RWD forward to provide support for effective regimens and potentially lead to FDA label changes. “If the payers can turn to the KOL and the agency and they say — there’s enough data here to support it—it doesn’t have to be [from] a randomized controlled trial, but there’s enough data to support it … then the payers can buy in,” he said.

Baljević added that educating practitioners and payers about RWE is needed to improve interpretation and uptake. “It takes quite a while for the randomized [controlled trial] data to permeate into [the] community and into the real world,” he said. “In many settings where we discuss some of these things, we often hear feedback from our colleagues [who] say, ’I didn’t realize that [these] data [were] there, and this is going to really impact how I use X [drug].’”

Baljević also said that RWE needs to be used proactively by practitioners and payers to anticipate future patient needs. For example, the upcoming approval of 4-drug regimens in the frontline setting (eg, D-RVd [daratumumab plus lenalidomide, bortezomib, and dexamethasone]) and introduction of CAR T-cell therapy and bispecific antibodies into the first- or second-line setting will change the characteristics of patients who develop RR disease. “After just 1 line of treatment, we’re going to have patients [who] are triple-class … [RR],” he stated. Baljević indicated that if randomized trial data are not available, RWE can provide information on how different populations of patients responded to a given treatment and inform practitioners and payers on upcoming challenges in the near future.

Beveridge added that using RWE to predict prognosis affects how payers approach paying for a therapy. For example, treatments that put people into maintenance for years are important to support, because they can potentially add several years of life. “There is an intrinsic, moral imperative for people to do that correctly in maintenance,” he said. “At the same time, in those patients who are maybe 80 years old [and] … have a large, long list of comorbidities where there’s no evidence that [they] are going to do particularly well, maybe we should be treating that group in a different manner … This is the power of RWE in this disease.”

**CLOSING REMARKS**

With the multiple effective treatments for MM, finding ways to use available resources in a cost-effective way is important moving forward. Improving the interaction between pharmacy benefit providers, payers, agencies, and practitioners will help deliver cost-effective therapies to the most appropriate patients. Furthermore, the confluence of computer and medical technologies will improve the ability to mine data and run multivariate analyses, which will advance knowledge among practitioners about the impact of the data and ways that data may guide treatment decisions.

**REFERENCES**


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