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The Role of Real-world Evidence in the Evolving Treatment Landscape of Multiple Myeloma

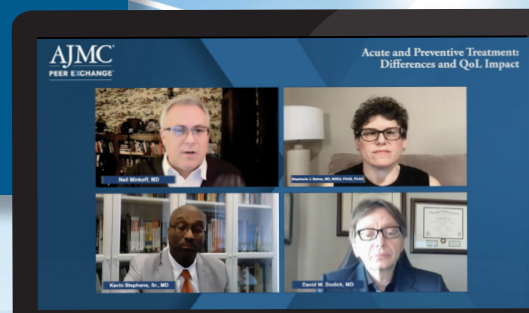
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Multiple Myeloma: Diagnosis and Treatment Options

MULTIPLE MYELOMA (MM), the second most commonly diagnosed hematologic cancer in the United States, is the uncontrolled proliferation of malignant monoclonal plasma cells in the bone marrow.^{1,2} MM is most frequently diagnosed among people aged 65 to 74 years (the median age at diagnosis is 69), men, and people of African American descent (2013-2017).² It is estimated that there were 32,270 new cases and 12,830 deaths from MM in 2020. The 5-year relative survival rate of MM (2010-2016) is 53.9%, with the median age at death being 75 years.²

To diagnose MM, practitioners must distinguish it from other plasma cell neoplasms/dyscrasias.³ In addition to the patient's history and physical examination, numerous studies are needed.³ To determine whether the patient's MM is symptomatic or asymptomatic, the National Comprehensive Cancer Network (NCCN) recommends a complete blood count, a peripheral blood smear, blood urea nitrogen and creatinine, creatinine clearance, serum electrolytes, liver function tests, serum calcium, albumin, lactate dehydrogenase, and β_2 -microglobulin.³

Along with these studies, the NCCN also recommends additional serum and urine analyses. The serum is analyzed to determine immunoglobulin levels, how much monoclonal protein is present (through serum protein electrophoresis), and the type of M protein involved (through serum immunofixation electrophoresis). This information enables practitioners to monitor disease progression and treatment response.³ Urine analyses include 24-hour total protein, urine immunofixation electrophoresis, and urine protein electrophoresis.³

Together with the previous studies, the NCCN also recommends the following studies:

- **BONE MARROW EVALUATION:** A bone marrow evaluation is necessary because a major criterion for diagnosing MM is whether the percentage of clonal bone marrow plasma cells is at least 10%.³
- **SERUM FREE LIGHT-CHAIN ASSAY:** The serum free light-chain assay is a sensitive way to screen for MM. It informs prognosis and is necessary to demonstrate stringent complete response according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.³
- **CYTOGENETIC STUDIES:** Cytogenetic studies can identify certain MM disease subtypes. Specific amplifications, deletions, and translocations have occurred in patients with MM.³
- **IMAGING:** Imaging detects bone disease. For the initial diagnostic work-up, the NCCN recommends fluorodeoxyglucose-positron emission tomography/computed tomography (CT) or whole-body low-dose CT. When preferred imaging is unavailable, a skeletal survey may be used.³

These study results can then be used to see whether the patient fulfills the criteria for MM (symptomatic). The diagnosis requires “clonal bone marrow plasma cells at least 10% or biopsy-proven bony or extramedullary plasmacytoma” and any CRAB criteria or SLiM biomarkers.³ CRAB criteria include calcium greater than 11 mg/dL; renal insufficiency (creatinine > 2 mg/dL or creatinine

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clearance less than 40 mL/min); anemia (hemoglobin < 10 g/dL or 2 g/dL < normal); and bone lesions.³ SLiM biomarker criteria include 60% or more clonal plasma cells in the bone marrow; involved/uninvolved free light chain (FLC) ratio at least 100 with the involved FLC being at least 100 mg/L; and MRI with “more than 1 focal marrow (nonosteolytic) lesion.”³

Fortunately, newer agents have demonstrated improved clinical outcomes or are under investigation for treating RRMM.

After a patient receives a diagnosis of symptomatic MM, they will first receive primary therapy.³ The NCCN’s preferred primary therapy options for transplant candidates include bortezomib/lenalidomide/dexamethasone and bortezomib/cyclophosphamide/dexamethasone.³ Nontransplant candidates are also eligible for many of the same regimens as transplant candidates.³ The NCCN prefers 3-drug regimens for their higher response rates and depth of response, but 2-drug regimens may be appropriate for patients who are elderly and/or frail.³

Those eligible for a transplant then receive high-dose chemotherapy and autologous hematopoietic cell transplant (HCT).³ Every patient should be evaluated for HCT. Depending on the setting, any of the following 3 types of HCT may be appropriate: single autologous HCT, tandem HCT (when a second course of high-dose therapy and HCT is given within 6 months of the first course), or an allogeneic HCT.³

Following primary therapy, patients begin maintenance. Under the maintenance therapy discussion, the NCCN highlights lenalidomide, bortezomib, and ixazomib. Single-agent lenalidomide is a preferred regimen.³ Although lenalidomide does not have the same neurologic toxicity as thalidomide, it does increase the risk of certain toxicities, including the rate of severe neutropenia and the risk of secondary cancer.³ Bortezomib is notable as an option for both transplant-eligible and -ineligible patients.³ Ixazomib is a category 1 “other recommended” therapy for those who are transplant eligible.³

MM almost invariably progresses or relapses, generally while patients are receiving therapy.⁴ The IMWG defines 3 types of relapse: clinical relapse, relapse from complete response (only if the end point is disease-free survival), and relapse from minimal residual disease (MRD) negative (only if the end point is disease-free survival).⁵

Each type of relapse is indicated by 1 or more of the specified criteria. Clinical relapse criteria include a hypercalcemia that is greater than 11 mg/dL; a decrease in hemoglobin of at least 2 g/dL that is not related to therapy or other nonmyeloma-related conditions; an increase in serum creatinine by 2 mg/dL or more from the start of the therapy that is attributable to myeloma; hyperviscosity related to serum paraprotein; a definite increase, which is defined as a 50% (and at least 1-cm) increase as measured serially by the sum of the products of the maximal perpendicular diameters of measured lesions in the size of existing plasmacytomas or bone lesions; development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); and direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder.⁵

Complete response criteria include the development of at least 5% plasma cells in the bone marrow; the reappearance of serum or urine M protein by immunofixation or electrophoresis; and the appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).⁵

Relapse from MRD-negative criteria include development of at least 5% clonal plasma cells in the bone marrow; loss of the MRD-negative state by evidence of clonal plasma cells on next-generation flow or next-generation sequencing, or positive imaging study for recurrence of myeloma; reappearance of serum or urine M protein by immunofixation or electrophoresis; and appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).⁵

Fortunately, newer agents including immunomodulators (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies (mAbs), histone deacetylase inhibitors (HDACis), chimeric antigen receptor (CAR) T-cell therapy, nuclear export inhibitors/selective inhibitors of nuclear export (SINEs), and bispecific monoclonal antibodies (BsMAbs) have demonstrated improved clinical outcomes or are under investigation for treating RRMM.⁶

Immunomodulators

The mechanism(s) of action for IMiDs are incompletely understood, but it is believed that they (1) break down intrinsic proteins by binding to cereblon; (2) promote myeloma cell cycle arrest and apoptosis by inhibiting oncogenes and increasing expression of tumor suppressor

genes; (3) inhibit angiogenesis, growth factor production, and the differentiation of osteoclasts; and (4) enhance natural killer (NK) cell activity and other immune effects.⁶ Thalidomide, lenalidomide, and pomalidomide are 3 IMiDs used to treat certain patients with MM.⁶

Thalidomide was initially approved in 1998 and has a black box warning for embryo-fetal toxicity and venous thromboembolism. It is indicated in combination with dexamethasone to treat patients with a new diagnosis of MM.⁷ It is the predecessor to lenalidomide and pomalidomide.⁶

Lenalidomide was initially approved in 2005 and has a black box warning for embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism. Its indications are less restrictive than those of other myeloma agents. For MM, it is indicated in combination with dexamethasone to treat adults. It is also indicated as a maintenance therapy for those who have received autologous hematopoietic stem cell transplantation.⁸

Pomalidomide was approved in 2013 and has a black box warning for embryo-fetal toxicity and venous and arterial thromboembolism. It is indicated in combination with dexamethasone for the treatment of MM in adult patients who have been treated with 2 or more therapies including lenalidomide and a PI but whose disease progressed within 60 days of completing their last therapy.⁹ Even in disease that is refractory or resistant to lenalidomide, pomalidomide can potentially elicit a response.⁶

Proteasome Inhibitors

Another class of agents used to treat patients with MM is the PIs. PIs work by interfering with the ubiquitin proteasome system to prevent protein recycling, eventually resulting in apoptosis.⁶ PIs are generally thought of as being “critical components of any regimen that is used to treat patients with high-risk myeloma or patients with renal failure.”⁴ The PIs used to treat MM include bortezomib, carfilzomib, and ixazomib, with marizomib under development.⁶

Bortezomib was the first PI approved in 2003.^{6,10} It is given parenterally, is reversible,⁴ and is indicated for the treatment of patients with MM and mantle cell lymphoma.¹⁰

Carfilzomib is a second-generation PI approved in 2012; it is not reversible and is given intravenously.^{4,6} It is indicated in combination with (1) lenalidomide and dexamethasone, (2) dexamethasone, or (3) daratumumab and dexamethasone for the treatment of RRMM in people who have already been treated with 1 to 3 lines of therapy.¹¹ It is also indicated as a single-agent treatment in people with RRMM who have been treated with at least 1 line of therapy.¹¹

Ixazomib is the first oral PI.⁶ It was approved in 2015 and is indicated in combination with lenalidomide and

dexamethasone to treat myeloma in patients who have been treated with at least 1 therapy.¹²

Marizomib is a PI in clinical development, with the latest trial in myeloma—a phase 1 trial—completed in 2016.^{6,13}

Monoclonal Antibodies

The development of mAbs has affected survival in both the up-front and relapse settings.⁶ The mAbs used to treat patients with MM include elotuzumab and daratumumab.⁶

Elotuzumab is an anti-SLAMF7 mAb whose Fc portion binds to CD16 receptors of NK cells, activating them to kill myeloma cells.¹⁴ Approved in 2015, it was the first mAb approved for RRMM; compared with other drugs, it has demonstrated modest improvements in overall survival (OS).^{6,15} It is not indicated as a monotherapy. Instead, it has approval for adult patients with MM in 2 combinations: (1) with lenalidomide and dexamethasone in those who have already been treated with 1 to 3 therapies and (2) with pomalidomide and dexamethasone in those who have already been treated with at least 2 therapies including a PI and lenalidomide.¹⁵

Daratumumab—an anti-CD38 IgG1 humanized mAb—kills tumor cells by targeting CD38 on myeloma plasma cells and modulating the immune system.⁶ It was approved in 2015 and is indicated for the treatment of MM both as a monotherapy and in multiple combinations.¹⁶ As a monotherapy, it is indicated in patients who have previously been treated with at least 3 lines of therapy including a PI and an IMiD or in those double-refractory to both a PI and an IMiD. Its 6 approved combinations vary not only by the agents with which daratumumab is combined but also by the patient populations in which they are indicated.¹⁶

Histone Deacetylase Inhibitor

Panobinostat is an HDACi that regulates intracellular protein homeostasis, the cell cycle, and apoptosis. HDACis may be synergistic with PIs given that they both lead to protein accumulation.⁶ Approved in 2015, panobinostat is indicated in combination with bortezomib and dexamethasone for the treatment of MM in patients who have previously been treated with at least 2 regimens including bortezomib and an IMiD.¹⁷ Panobinostat also has a black box warning for serious and fatal toxicities that include cardiac toxicities and severe diarrhea.¹⁷

CAR T-Cell Therapy

CAR T cell is a cellular therapy in which the patient's own T cells are removed and genetically modified to produce CARs, which are receptors that do not exist naturally and are able to attach to a tumor antigen. Once modified to have the specific CAR, the modified T cells are multiplied in a lab and then infused back into the patient.¹⁸

Idecabtagene vicleucel is the first B-cell maturation antigen–directed CAR T-cell therapy for patients with relapsed/refractory MM after 4 or more prior lines of therapy, including an immunomodulatory agent, a PI, and an anti-CD38 mAb.¹⁹ Approval followed the phase 2 KarMMA trial (NCT03361748) in which idecabtagene vicleucel had an overall response rate of 72% (95% CI, 62%-81%) and a stringent complete response rate of 28% (95% CI, 19%-38%) in patients with RRMM who had previously been treated with at least 4 lines of therapy.¹⁹ Idecabtagene vicleucel is given as a 1-time infusion and has a boxed warning for cytokine release syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, neurologic toxicities, and prolonged cytopenia.¹⁹

Nuclear Export Inhibitor/Selective Inhibitor of Nuclear Export

Selinexor is a first-in-class SINE that works by blocking XPO1, a protein that is often overexpressed in MM.²⁰ Selinexor was initially approved in 2019 and is now indicated in combination with bortezomib and dexamethasone to treat MM in adults who have previously been treated with at least 1 therapy; it is also indicated for use in combination with dexamethasone to treat RRMM in adults who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 immunomodulatory agents, and an anti-CD38 mAb.²¹

Bispecific Monoclonal Antibodies

BsMAbs are under investigation in MM; they bind to 2 different antigens at the same time, usually one on a T cell and the other on the tumor cell. In a way, BsMAbs are like CAR T-cell therapy in that they both use the host's own cells to target the neoplastic cells. However, BsMAbs can be available faster because they do not require the processing of CAR T-cell therapy.¹⁴ Three BsMAb platforms of note in clinical trials are the BiTE platform, DuoBody platform, and DART platform.¹⁴ The BiTE platform is made up of 2 single-chain variable fragments; one binds to CD3 on T cells, and the other binds to tumor.¹⁴ The DuoBody platform is used to develop bispecific antibodies able to connect with 2 different targets.^{14,22} The DART platform has diabodies reinforced with a C-peptide disulfide bond.¹⁴

Even though this discussion of agents is not exhaustive, a multitude of treatment options exist, with more agents in development. Nevertheless, PIs are considered a crucial component of regimens used to treat high-risk myeloma.⁶ And, along with PIs, IMiDs have significantly advanced and are fundamental to MM treatment.⁶ The introduction of PIs and IMiDs increased OS in patients with MM and changed how patients are treated.²³

For patients who are fit and younger, a PI and an IMiD are usually used in the first-line setting for induction, and

most patients with RRMM have been treated with drug combinations including a PI and/or an IMiD.⁶ Perhaps the more challenging question is regarding what to do next as patients relapse. As new agents are developed, treatment choices and potential combinations increase, bringing not only opportunity but also complexity.²⁴ Practitioners have not only doublets but also triplets, quadruplets, and other combinations from which to choose, often with more than 1 option within each of those categories.^{24,25}

Another part of treatment choice rests on sequencing, which is the order in which the patient receives treatments.²⁶ Trials have not compared most regimens head-to-head in MM, and determining ideal treatment sequence is an unmet need.²⁵

Although treatment guidelines provide recommendations, multiple choices remain. To facilitate navigating treatment choices, stakeholders can evaluate disease-related, patient-related, and treatment-related factors.

Finally, timing is one of the biggest challenges in treating RRMM, and it is also of critical importance.⁶ Research suggests that patients do better when treated in clinical trials or at specialty treatment centers. This may be due to regular monitoring, which enables prompt identification of biochemical relapse. Superior outcomes may be demonstrated when patients are treated earlier at the biochemical stage rather than later at the symptomatic stage.²⁷

Although treatment guidelines provide recommendations, multiple choices remain. To facilitate navigating treatment choices, stakeholders can evaluate disease-related, patient-related, and treatment-related factors.²⁵

The Patient

Age can influence treatment choice but should not be the only factor taken into consideration. An older patient who is fit may be appropriate for the same treatment as a younger patient.²⁵ Instead of using age alone, the IMWG developed an assessment tool to determine patient frailty/fitness. The geriatric assessment tool incorporates 4 parts: age, activities of daily living, instrumental activities of daily

living, and the Charlson comorbidity index.²⁵ It provides a patient score from 0 to 5 with 0 indicating fit, 1 indicating intermediate fitness, and 2 or higher indicating frail.^{25,28} Able to predict both the risk of toxicity and death in elderly patients with myeloma, the tool can inform the feasibility of a treatment regimen.²⁸

In addition to their inclusion in the IMWG assessment tool, comorbidities/organ function also need to be evaluated independently against a potential treatment regimen's possible toxicity.²⁵ The risk of cytopenias, for instance, is increased with certain PIs and IMiDs, but many elderly patients already suffer from cytopenias.²⁵ Therefore, practitioners need to be prepared to manage cytopenias, perhaps through dose reduction or interruption or with granulocyte colony-stimulating factor if febrile neutropenia is an issue.²⁵

Finally, the more subjective parameters of preference and quality of life also need to be considered.²⁵ Patients want to be able to continue their regular activities. When daily activities are compromised, patients tend to do worse, whereas preservation of routine is associated with less fatigue, fewer adverse effects (AEs), and better quality of life. Alternatively, when quality of life is compromised, treatment may be cut short.²⁷

The Disease

Treatment choices also hinge on disease qualities such as whether the patient experienced early or late relapse, for instance. Early relapse is considered that which occurs in patients who have received 1 to 3 lines of therapy, whereas late relapse is that which occurs in patients who have received more than 3 lines.²⁵ For early relapse, practitioners can start by determining whether the patient is refractory or sensitive to lenalidomide and/or bortezomib.²⁵ For late relapse, the main considerations are whether the patient is refractory to 3 or more agents and, if so, which ones.²⁵

Length of response to previous treatments also matters when determining later treatment. For instance, if the patient relapsed many months after being off therapy (therapy de-escalation is encouraged to minimize toxicity once patients have been stable long enough), then that same therapy can potentially be tried again.²⁵

Lastly, the risk status of the current disease needs to be determined.²⁵ The relapse could be a potentially less aggressive biochemical relapse, or patients who relapse may have developed genetic abnormalities they did not have earlier such as a *MYC* rearrangement, 1p deletion, 1q amplification, or 17p deletion, for instance. Genetic changes such as these can alter the patient's prognosis.⁴

Treatment

Pivotal to treatment selection in RRMM is what treatment the patient has already received. If the patient has never

had an autologous stem cell transplant (ASCT) or if the patient had a greater than 18-month-long progression-free survival (PFS) with a first ASCT, then practitioners should consider ASCT for those who are eligible.²⁵ Patients with an indolent relapse who responded well to ASCT before are candidates for salvage ASCT.⁴

Which treatment(s) the patient has already received is also critical because many of the agents' FDA-approved indications are defined by previous treatment. Pomalidomide, for instance, is indicated in patients who have already undergone at least 2 lines of therapy including lenalidomide and a PI.⁹ Idecabtagene vicleucel's label is even more stringent: It is indicated in patients with RRMM after 4 or more lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.¹⁹

When deciding which treatment to use next, providers should also consider how the patient tolerated earlier therapy and the length of response.⁴ Toxicities and comorbidities that have developed as a result of earlier treatment can complicate treatment at relapse.⁴

Lastly, availability can be an issue for patients. Patients may not be able to access a particular agent because of costs, inability to travel, or other issues.²⁷ On a related note, how the treatment is administered (eg, orally, intravenously, subcutaneously) is also an important consideration. Even if time without progression is shorter with an oral regimen or if the oral regimen has more potential AEs, patients may still prefer the convenience of this route, particularly if they cannot or do not want to go to a health care facility for infusions.²⁷

As new agents become available, treatment becomes more promising but also more complex.²⁵ Practitioners need to analyze patient, treatment, and disease factors to choose the treatment that is best for the individual patient.²⁵ Triplet regimens are generally preferable to doublets, but practitioners need to balance maximizing the potential for PFS and OS with minimizing toxicity and maintaining quality of life.²⁵ ♦

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The Contribution of RWE to the Management of Relapsed/Refractory Multiple Myeloma

IN DETERMINING SAFETY AND EFFICACY, randomized controlled trials (RCTs) are considered the gold standard.¹ RCTs can evaluate cause and effect and minimize bias through their prospective design, randomization, pre-defined end points, and minimization of confounders.² However, it is difficult to determine potential benefits for those who were excluded from trials.¹

Real-world data (RWD) and real-world evidence (RWE) are other forms of evidence that complement RCT data. The FDA defines RWD as “the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”³ These sources can include:

- Electronic medical records^{1,3-5}
- Administrative claims data^{1,3-5}
- Registries^{1,3-5}
- Hospital claims data¹
- Health surveys⁴
- Patient-reported outcomes⁴
- Wearable devices⁵
- Apps⁵

RWE is defined as “the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.” Just as there are different sources of RWD, different study designs or analyses can generate RWE. Examples can include pragmatic trials, large simple trials, and observational studies, which can be prospective or retrospective.³ In a retrospective observational study, investigators choose their study population and then use that population’s historical data that were collected prior to the start of the study. By contrast, in a prospective observational study, investigators collect data after they have identified their study population.⁶

End points of RWE studies may differ from those of RCTs and can include time to next treatment (TTNT), which can be used as a proxy for progression⁷⁻⁹; evaluation of real-world treatment patterns and outcomes⁷; health care resource utilization^{10,11}; and budget impact and cost-benefit models using total cost of treatment.^{7,12}

Value Provided by RWE Studies

RWE studies add value by complementing the data generated by RCTs.¹ Because RWE studies can utilize large sample sizes and cover longer time periods, they have the

potential to reveal adverse medication effects not detected in the initial trials.¹ For example, the FDA uses RWE to continue evaluating drug safety after approval.⁶

RWE studies are also more generalizable to the wider population, enhancing external validity.^{1,2} According to de Lusignan and colleagues, “Whilst RWD are inherently more messy, their advantage is that RWE studies will include people with multimorbidity, on usual prescribed doses, and standard patterns of adherence” as well as the “thresholds at which treatments are implemented.”¹

By including patient populations that may not have been studied prior to approval, RWE studies help stakeholders better understand the treatment’s risks and benefits under real-world conditions.^{1,6} In particular, these questions can be relevant to health care decision-makers.⁴ RWE represents the patient population that insurers are covering as well as the environment in which the patients are treated.⁴ Payers can use RWE to inform decision-making on multiple levels including formulary placement and determination of necessity.⁴

Limitations

Comparing care pathways, especially in medically complex patients, remains challenging.¹ RWE cannot confirm causality, though statistical methods can take confounders into account and control for bias; how to best minimize bias remains to be determined.^{1,5,6}

Because reducing bias shores up confidence in results, organizations have created and are creating guidelines and legislation for RWE study best practices.^{3,5,6} Orsini and colleagues note, “As the potential use of RWE to support decision-making for market authorization, reimbursement, and clinical guideline development grows, the need to trust that evidence grows correspondingly.”⁵ Among others, US lawmakers, the FDA, and a joint Special Task Force of the Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) have put forth guidance to optimize the use of RWE.

At the legislative level, The Food and Drug Administration Modernization Act of 1997 (FDAMA 114) and the 21st Century Cures Act (Cures Act) have provided relevant guidance. FDAMA 114 provided for communication about health care economic information not found in the product label.¹³ The Cures Act, which was signed into law in December 2016, clarifies language contained in FDAMA 114 and facilitates making medical advances

available to patients sooner. The Cures Act does this by laying the groundwork to determine the power of RWE (1) to facilitate the approval of additional indications for drugs that are already approved or (2) to fulfill or supplement required postapproval drug studies.^{6,14}

Within its RWE Program, the FDA has also developed a guiding framework. Among other things, the framework highlights how RWD can make clinical trials more efficient by⁶:

- Assembling geographically distributed research cohorts (eg, in drug development for rare diseases or targeted therapeutics)⁶
- Assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial site⁶
- Generating hypotheses for testing in randomized controlled trials⁶
- Identifying drug development tools (including biomarker identification)⁶
- Identifying prognostic indicators or patient baseline characteristics for enrichment or stratification⁶
- Informing prior probability distributions in Bayesian statistical models⁶

As part of its real-world evidence program, the FDA will also assess quality control to ensure that RWD/RWE and their uses meet the FDA's standards.⁶

The ISPOR/ISPE joint Special Task Force strives to improve the uptake of RWE by increasing the transparency of RWE studies so that they can be independently evaluated. To this end, the Special Task Force made the following recommendations on “good practices” in RWE studies: (1) Investigators should communicate at the beginning whether their study is to generate a hypothesis, or whether it already has a hypothesis that needs to be tested in a specific population; (2) before analyzing their data, investigators should publicly post, in a registry, their study protocol and how they plan to analyze the data; and (3) when publishing their results, investigators should provide an “attestation of conformance or deviation from the initial study protocol and analysis plan.”⁵ Following their issuance of “good practices,” the Special Task Force also joined with other stakeholders to identify ways to optimize RWE registration.⁵

Given the utility of RWD/RWE, it is instructive to see how RWD/RWE have been employed in the realm of multiple myeloma (MM). In their review, Terpos and colleagues highlight the gap between efficacy—“performance under ideal, controlled conditions” (ie, a clinical trial)—and

effectiveness or “performance of a regimen under real-world conditions.”¹⁵ They found that there are many potential reasons for this gap. For one, about 40% of patients with MM do not qualify for phase 3 clinical studies and are therefore unrepresented.¹⁵ Secondly, regimens have become more complex. They contain novel drugs and may be more toxic than previous regimens. Without RWD, it is difficult to know how feasible these regimens are and how adherent patients can be.¹⁵ Lastly, treatment goals change from patient to patient depending on patient-, treatment-, and disease-specific factors.¹⁵

To make data collection better, Terpos and colleagues suggest that stakeholders expand clinical trial eligibility criteria, collect real-world along with clinical trial data, standardize patient reported outcome data collection, and disseminate optimal treatment information from specialty treatment centers.¹⁵ By supplementing clinical trial data with RWD on efficacy and safety, quality of life, economic impact, satisfaction with treatment, and patient preference, treatment choices could be better informed.¹⁵

To capture what matters to patients in the real world, Terpos and colleagues identified symptom burden; adverse effects (AEs)/toxicities; quality of life including daily and physical activities; treatment cost (ie, the financial toxicity); level of convenience, including how treatment is administered (eg, oral treatment makes it easier to work, continue with daily activities); and comorbidities as factors of importance.¹⁵

Incorporating RWD may improve treatment effectiveness. For example, a patient may be more likely to persist on a more convenient, tolerable treatment that provides better quality of life.¹⁵ To improve comparisons of regimen effectiveness, more patient-related factors and endpoints need to be considered. To make comparisons using these RWD more valid, stakeholders also need to standardize how these data are compiled, reported, and analyzed.¹⁵

In another real-world study, Chari and team wanted to compare outcomes and treatment choices in patients with relapsed/refractory MM (RRMM) across 3 regimens. These RWD are needed because of the shortage of head-to-head studies for these regimens; many patients with MM are older (ie, the type of patient excluded from clinical trials), and older patients also tend to have comorbidities that increase their risk of negative outcomes.¹⁶

The 3 regimens included in the study were bortezomib plus lenalidomide/dexamethasone (VRd), carfilzomib plus lenalidomide/dexamethasone (KRd), and ixazomib plus lenalidomide/dexamethasone (IRd).¹⁶ To compare the regimens, the investigators used TTNT, a surrogate for progression-free survival (PFS); frailty, which can be prognostic in patients with MM; and TTNT by frailty. They also examined how patient-, disease-, and treatment- related factors affected treatment choice.¹⁶

They found that, in line of therapy (LOT) 2 or later, the risk of regimen discontinuation was significantly lower for those treated with IRd than KRd (HR, 0.71; $P = .0209$).¹⁶ The risk of discontinuation was also lower compared with regimens containing bortezomib (HR, 0.85).¹⁶ They also found, in LOT 2 or later, the risk of discontinuing part of the regimen (the proteasome inhibitor [PI] or lenalidomide) was lower for regimens containing ixazomib. For IRd versus KRd, the HR was 0.65 for discontinuing the PI ($P = .0034$) and 0.64 for discontinuing lenalidomide ($P = .0015$).¹⁶ For IRd versus VRd, the HR was 0.62 for discontinuing the PI ($P = .0003$) and 0.75 for discontinuing lenalidomide ($P = .0312$).¹⁶ For KRd versus VRd, however, the risk was comparable; the HR was 0.94 for discontinuing the PI and 1.18 for discontinuing lenalidomide ($P > .05$ for both).¹⁶ TTNT was comparable between the 3 regimens in LOT 2 or later.¹⁶

In subgroup analyses of patients with a modified frailty score of intermediate to frail, the risk of death or starting another LOT was also lower in those treated with IRd versus KRd (HR, 0.70; $P = .0389$).⁶ In those treated with KRd versus VRd, however, the risk was higher (HR, 1.38; $P = .0481$).¹⁶ There was not a significant difference in this population between those treated with IRd or VRd.¹⁶ However, there was a significantly higher risk in the IRd versus KRd group (HR, 0.70; $P = .0389$) and the KRd versus VRd group (HR, 1.38; $P = .0481$).¹⁶ No adjusted TTNT differences were seen among fit patients.¹⁶

For regimen choice, high cytogenetic risk and prior immunomodulator (IMiD) exposure were independently associated with a significantly increased likelihood of treatment with IRd over VRd ($P < .02$).¹⁶ Symptomatic relapse, relapse after transplant, prior PI exposure, and being refractory to last prior therapy were significantly associated with choosing KRd over IRd; prior IMiD exposure, however, was independently associated with a significantly increased chance of treatment with IRd over KRd ($P < .02$).¹⁶ For KRd versus VRd, high-risk cytogenetics, symptomatic relapse, peripheral neuropathy, prior transplant history, prior PI exposure, and prior IMiD exposure were all significantly associated with an increased likelihood of treatment with KRd over VRd ($P < .04$).¹⁶

The investigators concluded that these results suggest that effectiveness is not as high in the real world as it is in clinical trials, which may be due to the number of patients who do not meet the trial eligibility criteria. They also suggest that tailoring treatment to the individual patient and taking things such as frailty into consideration could improve outcomes, especially considering the number of elderly patients with RRMM.¹⁶

Like Chari and team, Davies et al also compared triplets, including not only those containing PIs but also those containing daratumumab. Bortezomib has been the

traditional backbone for triplets used to treat RRMM. However, since bortezomib's approval in 2003, the PI carfilzomib was approved in 2012, and the PI ixazomib and the monoclonal antibody daratumumab were both approved in 2015, shifting the treatment landscape.¹⁷⁻²¹

To compare the effectiveness of bortezomib, carfilzomib, daratumumab, and ixazomib when incorporated into triplets used to treat patients with RRMM, Davies and colleagues completed a retrospective cohort study using data from 2007 to 2018 from Optum's deidentified electronic health records database.²¹ The database includes 6500 clinics in 50 states and is expected to reflect the general population.²¹ Qualified patients were adults with a MM diagnosis who had been treated with at least 1 LOT and then began a triplet regimen containing bortezomib, carfilzomib, daratumumab, or ixazomib combined with either an Rd or pomalidomide plus dexamethasone backbone on or after January 1, 2014.²¹ The primary outcome was TTNT (time from the start of the index regimen to initiation of subsequent LOT or death, whichever occurred first), a surrogate for PFS in real-world studies.²¹ The index regimen's duration of therapy, the time from initiation of the index regimen to discontinuation of the last drug in the regimen plus a run-out period, was an additional outcome evaluated.²¹ Patient-LOT was the unit of measure; the first date that each triplet regimen was initiated in LOT 2 or later was the index date for each triplet LOT of interest.²¹

In the stratified analysis for LOT 2 or later, median TTNT was also stratified by regimen with triplets containing ixazomib having the longest TTNT (11.1 months), followed by those containing bortezomib (9.8 months), daratumumab (7.2 months), and carfilzomib (6.7 months).²¹ Compared with regimens containing bortezomib (reference), the risk of next treatment initiation or death was also significantly lower with regimens containing ixazomib (HR, 0.80; $P = .0299$); it trended toward being significantly higher with carfilzomib regimens compared with bortezomib regimens (HR, 1.15; $P = .0529$). There was not a significant difference between daratumumab- and bortezomib-based regimens (HR, 1.04; $P = .6567$).²¹

However, on adjusted analyses for LOT 2 or later, there was no significant difference between regimens for risk of next treatment initiation or death compared with bortezomib-based regimens.²¹

When looking just at triplets using a lenalidomide/dexamethasone backbone or a pomalidomide/dexamethasone backbone, investigators found that the risk of next treatment initiation or death was significantly higher with carfilzomib plus lenalidomide/dexamethasone compared with bortezomib plus lenalidomide/dexamethasone (reference).²¹ However, in adjusted analyses, there was no significant difference.²¹ When evaluating a pomalidomide backbone, no significant differences were seen.²¹

The authors concluded that median TTNT was longest for triplets containing ixazomib compared with those containing bortezomib, daratumumab, or carfilzomib. However, on adjusted analyses, no significant difference was seen between any of the triplets for risk of next treatment initiation or death at LOT 2 or later. No significant difference was found either on the exploratory analysis of regimens with a lenalidomide/dexamethasone or pomalidomide/dexamethasone backbone. The investigators suggest more research is needed to improve understanding of differences between clinical data and real-world results.²¹

Because little is known about the cost of triplet regimens because of their relatively recent approval, Hollman and colleagues analyzed the real-world cost of 5 triplet regimens used to treat RRMM.²² The investigators realized that stakeholders including professional groups such as the American Society of Clinical Oncology and pharmacy benefit managers can use these data to assess the value of an intervention. As health care costs rise, this type of information can be used to keep cost in mind while still optimizing patient outcomes.

In their 1-year cost analysis, they estimated duration of treatment using PFS and evaluated 5 National Comprehensive Cancer Network–recommended and FDA-approved regimens²²:

1. Daratumumab plus lenalidomide plus dexamethasone (DARA/LEN/DEX)
2. Daratumumab plus bortezomib plus dexamethasone (DARA/BOR/DEX)
3. Elotuzumab plus lenalidomide plus dexamethasone (ELO/LEN/DEX)
4. Carfilzomib plus lenalidomide plus dexamethasone (CAR/LEN/DEX)
5. Ixazomib plus lenalidomide plus dexamethasone (IXA/LEN/DEX)

To evaluate cost, they analyzed administration costs, costs associated with AEs, comedICATIONS and 1-time costs, drug acquisition costs, monitoring costs, and subsequent therapy costs.²²

Finally, to estimate costs, the investigators used the RED BOOK for wholesale acquisition cost²²; the RED BOOK and Ollendorf and colleagues' report to determine subsequent costs²²; the Centers for Medicare & Medicaid Services 2018 Physician Fee Schedule to determine the cost of administration²²; the Centers for Medicare & Medicaid Services nonfacility national payments to determine the cost of monitoring and the cost of comedICATIONS²²; and Roy and colleagues' RRMM cost analysis along with AE rates included in the prescribing information for each triplet to determine the cost of managing AEs.²²

The investigators found that the greatest contributors to cost were the acquisition of the drug and treatment length.²² From least to most expensive, the base case average monthly cost per patient by triplet was²²:

1. DARA/BOR/DEX: \$13,890
2. IXA/LEN/DEX: \$22,231
3. ELO/LEN/DEX: \$24,322
4. DARA/LEN/DEX: \$26,410
5. CAR/LEN/DEX: \$27,432

They concluded that the lowest cost per patient for 1 year of treatment appeared to be DARA/BOR/DEX, whereas CAR/LEN/DEX appeared to be the most expensive. They also cautioned that the data were modeled; therefore, data on real-world treatment patterns would improve our understanding of the cost of triplet therapy. Nevertheless, the current study is informative for health care stakeholders.²²

To continue adding to the data on recently approved MM treatments, Bruno and colleagues retrospectively evaluated data from over 350 community oncology providers in a longitudinal, 2-phase study to evaluate real-world treatment patterns and outcomes in patients with RRMM treated with at least 2 lines of therapy.²³ The objectives were to describe treatment regimens and sequence, describe therapy lines, assess AEs, and evaluate outcomes through median real-world PFS (rwPFS) and median real-world overall survival (rwOS) across lines of therapy and by “older” versus “newer” treatments.²³ The investigators presented the data descriptively without statistical analyses.²³

The authors reported the following results. For first-line treatment, patients most commonly received bortezomib (n=357 of 456, 78.3%) and lenalidomide (n=278 of 456, 61.0%).²³ From first- to fourth-line treatment, median rwPFS decreased from 12.0 months to 2.9 months, and median rwOS decreased from 48.2 months to 7.8 months.²³ When outcomes were stratified by newer (bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, panobinostat, and pomalidomide) versus older agents, investigators found that newer agents had numerically higher rwPFS in first- and second-line usage, although 95% CIs overlapped.²³ Newer agents also had numerically higher rwOS across all lines, but again, 95% CIs overlapped.²³ Although lenalidomide and bortezomib were the clear choices in earlier lines of therapy, by the third-line setting, no therapy dominated, likely because of a lack of defined treatment pathways.²³

Bruno and colleagues concluded that clinical benefit seems to lessen with time, seeing as how TTNT and therapy duration usually decreased with more lines of treatment.²³

In the real world, the number of patients relapsing is probably higher than what has been seen in clinical trials, underscoring the need for more treatment choices.²³ Newer agents may be better than older agents at increasing rwPFS and rwOS especially as part of earlier treatment lines, but more research is needed.²³ The authors conclude that this study highlights the importance of incorporating new treatments early into treatment regimens in the real-world setting so a wide range of patients can benefit from their use.²³

To ensure the best outcomes for patients with RRMM, RWD and RWE studies are needed to complement clinical trial data.

Braunlin and colleagues also used recent RWD to evaluate MM trends and outcomes given all the new MM treatments and regimens.²⁴ They conducted a retrospective cohort study using data on patients with MM from Flatiron Health electronic health records from 2011 to 2019.²⁴ The primary research objectives were to describe patients' demographics and clinical qualities as well as how MM treatments/regimens varied by LOT and year.²⁴

They found that, in 10,553 patients, the use of doublets—either an IMiD plus dexamethasone or a PI plus dexamethasone—decreased, whereas the use of a triplet—a PI plus an IMiD plus dexamethasone—increased.²⁴ By 2018-2019, across all lines of treatment, triplets replaced doublets as the most frequently prescribed regimen: first line = 61.6%, second line = 44.1%, third line = 41.6%, fourth line = 41.7%, and fifth line or later = 34.0%. The most dramatic decrease in the use of doublets was in the front-line setting, where their use dropped by almost half by the study's end.²⁴ Not surprisingly, the investigators also found that the use of triplets specifically containing monoclonal antibodies increased following their 2015 approval.²⁴

According to the authors, “approval of these new agents increased the number of treatment options and paved the way for more complex drug class combinations. However, even with these new therapies and combination regimens, patients continue to relapse and additional efficacious and safe therapies are needed in this highly complex patient population.”²⁴

To ensure the best outcomes for patients with RRMM, RWD and RWE studies are needed to complement clinical trial data. Up to 40% of patients with myeloma do not qualify for phase 3 trials; therefore, how to best treat these patients remains to be seen.¹⁵ RWE studies include patients unrepresented in clinical trials under real-world treatment conditions, and they bring gaps between trial and real-world results into focus.^{1,15} This knowledge can then be used to optimize MM treatment going forward. ♦

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The Increasing Use and Importance of RWE

A Q&A With Faith Davies, MD, MRCP, MRCPATH, FRCPATH



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The American Journal of Managed Care® (AJMC®): In general, how important is real-world evidence (RWE)?

DAVIES: RWE is becoming more and more important. I think it was often previously treated as soft data. At the moment it hasn't reached the same level of importance as randomized phase 3 studies, but it's clearly becoming more important, so much so that the regulatory authorities are now paying attention to it and are asking for it to help support the drugs' effectiveness in the general clinical setting.

AJMC®: How does RWE complement randomized clinical trial (RCT) data?

DAVIES: For RCT data, we are essentially looking to see the efficacy of the drug: "Can it work? Is it better than the previous standard therapy?" These kinds of studies are performed in a very controlled environment. I would argue that real-world data are different. Rather than asking, "Can it work?" RWE is asking, "Does it work? What's its effectiveness?" What happens in the general clinical setting? It is efficacy versus effectiveness. For cancer trials, it's generally a small percentage of patients who actually make it into a cancer study. It is somewhere less than 5% of patients, so we need to have some way of ensuring that the data we're taking from our clinical trials show how it actually works for the other 95% of patients who haven't had the opportunity to take part in those studies. I would argue that the question is, "Can it?" versus "Does it?"

It is definitely important to have both RWE and RCT data because of the 95% of patients who are not in the initial studies for various reasons. Some of our patients in clinic will be very similar to those patients in the initial studies, but many of them will have unfortunately been excluded for reasons that are common in general patient populations. It's important to know that the drug is effective in these excluded patients as well.

AJMC®: How widespread is the use of RWE at your institution?

DAVIES: I'm fortunate that my institution is making a real move forward to look at real-world data. There's a lot of background work going on at the moment to enable the IT [information technology] infrastructure to be able to work through electronic medical records (EMRs) in a research capacity that's HIPAA [Health Insurance Portability and Accountability Act] compliant and is not going to be causing any confidentiality breaches. To date, most of the existing real-world data have been collected via registry databases that people have developed; some of those have been academic registries while others have been clinical trial registries or registries developed by nonprofit organizations. Another good source of real-world data is billing and insurance claims databases.

To some extent, true real-world data are from the EMRs. There have previously been a lot of small studies, but I now think that many hospitals and academic institutions are embracing RWE and are embracing technology that enables people to determine how their own practice is comparing with randomized clinical trials and with other available data sets. I think that's a good thing.

It is a good auditing tool and it helps move research and patient care forward. It's always important to make sure that what you think you're doing is actually what you're doing and to know the outcome of your interventions.

AJMC®: How can RWE best be used?

DAVIES: Within my disease space, it is becoming increasingly used to aid patient and doctor decision-making and from a regulatory perspective. We are finding that the number of uses is increasing, and therefore having RWE available to the community and having it talked about are very important.

For example, a number of nonprofit patient organizations now offer patients the opportunity to put their data into a database. Patients can then search for other patients like them. For instance, if they're starting on a new regimen, they can search to see what other patients have experienced in terms of adverse effects and how they managed them. It's not just for physicians and pharmaceutical companies; the patient side of things is important too.

From a regulatory perspective, it's key because, unfortunately, many of our drugs are very expensive, so having real-world data enables a further judge of quality and value. The benefit of the drug for the patient is sometimes easier to see in a real-world data set because you can often look at changes in frequency, delays, and time on therapy. You can also look at tolerability with respect to how long a patient stays on the drug or whether the doses of the drug are changed. A great example of this is Velcade [bortezomib]. Originally, all the clinical studies have the dosing schedule as days 1, 4, 8, and 11 of a 21-day cycle; whereas in the real world, we use it once every week so that adverse effects for patients, such as neuropathy, are much less. The tolerability is much better, and the efficacy is much better. We therefore learn a lot from looking back at those real-world data as far as how we can best treat our patients. Getting the messages out there about its importance is good. For the regulatory authorities, thinking about RWE data in the same sphere as phase IV data, ie, additional data on safety and effectiveness, is key too.

AJMC®: Are there potential concerns regarding the use of RWE?

DAVIES: There's still some skepticism around the control and the authenticity of the data. The only potential way to overcome this is to start using it and to test it against known standards. I think of RWE like phase 4 clinical study data. We often learn a lot from phase 4 studies, especially about safety, whereas RWE is more about treatment effectiveness

in the wider population. RWE is important because we are taking a wider patient group into consideration, which may not be the ideal patient population that was placed in the clinical trial. We have patients in the real world who have comorbidities or other issues going on; we are embracing this because the real-world data may reflect the general patient population more so than that ideal RCT group.

AJMC®: What are some examples of how RWE can be useful in the RRMM population?

DAVIES: Patients with relapsed-refractory myeloma tend to be slightly older and often have comorbidities. There have now been a number of studies where [investigators] have used their registry data to say, "Looking through my registry data, how many of the patients in my EMRs would make it into one of the randomized clinical studies?" The reality is that anywhere between 20% and 60% of patients would not make it into one of those clinical studies. That is usually because of comorbidities; it might be performance status, cardiac issues, or kidney issues. Many of these comorbidities may not be high-grade or complicated, but they take many patients out of that standard category of trial patients.

In addition to patients being excluded from clinical trials based on comorbidities, a number of groups of patients are often not well represented in our clinical trials. Examples include patients who are frail and older or patients from racial minority populations. This highlights that some practical reasons such as travel or distance to the trial site and socioeconomic factors are just as important as comorbidities. In addition, we know that hypertension and diabetes are often higher in African Americans. While those are not an issue with trial entry per se, these conditions must be well controlled to be able to get into the clinical study. Therefore, this often makes it more difficult for patient groups such as African Americans or the elderly or frail population to enter into a trial.

Having RWE data are key because they guide everyday clinical practice more than just stating whether the treatment works. It's helpful for when you have a typical patient sitting in front of you in clinic to think, "What do the real-world data tell me? I know my clinical trial tells me this should work, but when I look at typical patients, is it going to work?" People are often afraid that the clinical trial data won't be reflected in the normal everyday situation. There are now quite a few studies showing that the drugs sometimes work better or at least equally effectively when you have them in this wider group than they do just with patient groups in the clinical trial. ♦

Understanding How RWE Can Affect the Management of Myeloma

A Q&A With Robert M. Rifkin, MD, FACP



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The American Journal of Managed Care® (AJMC®): From your perspective, how can real-world evidence (RWE) be used to gain insight into the field of myeloma?

RIFKIN: Over the years, we've collected a large amount of data in multiple myeloma research registries, which is often the foundation for some of the RWE in myeloma. What we've found is that approximately 40% of a representative sample of [patients with] myeloma were actually not eligible for clinical trials to advance the field. The reason they weren't eligible was largely that the inclusion and exclusion criteria of the trials were too narrowly focused. With very specific questions in mind, we had actually excluded a significant number of real-world [patients with] myeloma. In addition, RWE also helps us to work with various manufacturers and various stakeholders of new myeloma therapies to help them understand perhaps where their therapy might fit in the patient's myeloma journey.

AJMC®: Can you describe how RWE can contribute to future studies in the myeloma space?

RIFKIN: As we move forward, RWE will help us design more appropriate and more user-friendly, for lack of a better word, clinical trials. In medical oncology only 3% or so of our patients enter research trials; as things get more and more specific with targeted therapy, that percentage might become less. So RWE actually helps us explore potential study populations. When we bring a new myeloma therapy online, RWE will have helped us survey the landscape and can hopefully identify a clinical trial that will accrue rapidly and be relevant.

Initially people really didn't value RWE, but there has been a change in the mind-set of the FDA and other regulatory agencies so that you can now use RWE as a foundation for designing clinical trials. And I think that's really advancing the field. This will enable clinical trial designs to be much more applicable to a generalizable population with multiple myeloma. In addition, we're also actively involved in developing synthetic controls, which is a control population from within our evidence database, almost like a simulation to use RWE and help us design relevant clinical trials.

AJMC®: What characteristics of RWE studies can increase their quality and credibility?

RIFKIN: A lot of real-world studies, at least in my experience, take several forms. Initially, before you can do any of these, you have to do a feasibility study so you can see whether, for example, in my network, there are enough people with multiple myeloma. After you perform that basic assessment, you have to conduct an evaluation to see what's available in the electronic health record because those are data points that are relatively easy to extract. Probably the most important step at the end of the day, once you've done all that, is to validate what you're doing. Our group will then go in and do very careful chart reviews. We're now starting to look at ways to automate the chart review

process with artificial intelligence and natural language processing. This exercise allows examination of the data set for its robustness.

In short, demonstration of feasibility of eligible patients with myeloma in the network or the group you're going to study creates the foundation and must ensure that all of the study population have electronic health records. Within our group, we give careful consideration to the methodology of how to conduct the study properly and efficiently to get out of it answers to the questions at hand in a credible and nonbiased way.

AJMC®: How can RWE contribute to the treatment decisions made by clinicians for the population with relapsed/refractory multiple myeloma?

RIFKIN: The vast majority of decisions in the relapsed/refractory population are being dictated by clinical practice guideline and adherence to clinical pathways. It's not likely you can immediately take RWE and generalize it to how you're treating your patients. In the setting of relapsed/refractory myeloma, we tend to, as in most of oncology and hematology, employ evidence-based decision-making. So within our network, we follow the [National Comprehensive Cancer Network] guidelines. There is also an additional layer, which is the value in terms of economic impact and cost of care. So if, for example, you have 2 treatments that are equally effective but one is half the cost of the other, you would most likely pick the less expensive one. At some point, I do see RWE being integrated into clinical trial design and into the pathways, but that's quite a ways away.

AJMC®: Is there a need for education regarding how RWE could be used in informing decisions?

RIFKIN: Overall both providers and patients are vastly undereducated about RWE. A lot of folks probably don't fully understand what we do to accumulate it to create the projects and the studies. Hopefully, we can push things forward into the clinic as we design research trials to improve patient access and decrease cost.

In general, there is still a lot of education to be done in medicine. And there's probably even more education that needs to be done in terms of RWE and how it plays into medical oncology and hematology decision-making. Overall, there's a huge lack of education regarding what you can reasonably expect for conclusions from a real-world study and how to apply that into trial design and into

practice. Stakeholder education and understanding how to interpret the published literature is vital to the integration of RWE into clinical practice.

AJMC®: What role does data adjustment play in the analysis of real-world data?

RIFKIN: One of the things that we commonly deal with in RWE is missing data points or disparities among the group under study. And then, of course, everybody wants to adjust for this. Along the way, we need to have access to unadjusted data as a first step. At the time of publication, multiple statistical methods need to be reviewed and validated to be sure they're appropriate and that you make appropriate adjustments. You can keep performing statistical adjustments forever, if you will, to get what you need, and that's the wrong approach. There really needs to be a balance, but I think you'll never see a study published that's completely "unadjusted."

AJMC®: Which study end points do you think are most relevant from an RWE standpoint, and are there some additional alternative end points that could be used for RWE studies?

RIFKIN: In the past, in myeloma trials, the "gold standard" has been overall survival. If you examine the myeloma landscape at present, we're doing so much better with all of our new therapies ([bispecific T-cell engager] molecules, [chimeric antigen receptor T cells], monoclonal antibodies, selective inhibitors of nuclear export proteins, and [histone deacetylases]) that overall survival is no longer realistic as an end point. So I think you need to not look entirely at overall survival, but we need to be looking at progression-free survival (PFS), and there's PFS1 and PFS2, which is the second PFS defined by statisticians.

Time to next treatment is really important because now we get people in plateau phases that are lasting for many months to years. A new entrant into the myeloma arena is detection of minimal residual disease (MRD) by next-generation sequencing of multiparameter flow cytometry. MRD is starting to be looked at as a surrogate end point [because] it's a lot faster to determine than waiting for an overall survival end point to mature, or even at PFS. We need to closely examine time to next treatment and what the PFS2 is, and how they integrate into the development of RWE. As a patient's myeloma journey proceeds, time between relapses tends to decrease, and the integration of RWE will soon make a significant clinical impact. ♦

