Integrating Best Practices to Improve Outcomes in Relapsed/Refractory Multiple Myeloma

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Abstract

Amy E. Pierre, MSN, ANP-BC, and Joshua Richter, MD, break down the approved and emerging treatment options for relapsed/refractory multiple myeloma, including mechanisms of action, supporting clinical data, and associated adverse events, and discuss best practices for selecting and sequencing therapy.

Emerging treatments for relapsed/refractory multiple myeloma (RRMM) include options beyond triplets, including immunotherapy and mutation-driven therapy. In the treatment of RRMM, advanced practitioners should employ risk-adapted treatment strategies with the most effective available agents, tailor the prevention and management of treatment-related toxicities to the individual, and understand the emerging data for new therapies on the horizon—poised to incorporate them once they become approved.

These topics were discussed at JADPRO Live 2019 by Amy E. Pierre, MSN, ANP-BC, of Memorial Sloan Kettering Cancer Center, New York, and Joshua Richter, MD, of Tisch Cancer Institute and Icahn School of Medicine at Mount Sinai, New York.

"NOT A SINGLE DISEASE ENTITY"

Dr. Richter reminded attendees that multiple myeloma "is not one disease," but a "clonally heterogeneous disease" that varies among individuals. At diagnosis, most patients already demonstrate four to six subclones of disease that become dominant or recessive as patients go through treatment. "Variability in clones and in risk means we need drugs with multiple mechanisms of action to kill cells. This is why triplets and even quadruplets have become the standard, because one or two drugs may only control some of the clones," he explained.

Ms. Pierre noted that with contemporary treatment, heavily pretreated RRMM patients now have a median overall survival after relapse of about 8 months. If they become "penta-refractory" to all three major

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classes of drugs (proteasome inhibitors, immunomodulatory drugs [IMiDs], and monoclonal antibodies), however, this drops to 3 months or less. "We need new treatment targets to combat this problem," she said.

The "penta-refractory" patients represent an unmet need, as do elderly and frail patients, she said. Also needed are better access to treatment for African Americans, better symptom management (especially for pain and neuropathy), "and a cure!"

CURRENTLY APPROVED TREATMENTS

Table 1 shows the wealth of drugs currently approved for RRMM (and in some cases, newly diagnosed), with new drug approvals happening at a fast pace. "Across the past 11 years, we've had 11 drugs, but this is accelerating," Dr. Richter said. "Four drugs or therapies are slated to be approved in 2020, including several others that might be approved along with new combinations."

For the main drugs currently in use, Ms. Pierre described what she called "advanced practice considerations." For IMiDs, clinicians can help prevent adverse events through compliance with Risk Evaluation and Mitigation Strategies (REMS) programs (including pregnancy testing and contraception requirements), monitoring blood counts, educating patients regarding infection risks, understanding renal dosing of lenalidomide, assessing risk of venous thromboembolism (VTE; possibly using the SAVED score, a new risk assessment model (Li et al., 2019), and ensuring appropriate prophylactic anticoagulation.

Describing the proteasome inhibitors, she noted that, unlike bortezomib, carfilzomib and ixazomib are used exclusively in the relapsed setting; both are approved for first relapse. Advanced practice considerations for carfilzomib are to premedicate, use intravenous hydration prior to cycle one (for prevention of tumor lysis syndrome), employ prophylaxis for VTE and zoster, monitor blood counts, and do a cardiac evaluation to prevent new or worsening of preexisting cardiac failure (and to evaluate breathing/coughing issues). Considerations for ixazomib are to monitor blood counts, give antiviral prophylaxis, risk assess for VTE and give prophylaxis if lenalidomide is used, and premedicate with dexamethasone. Gastrointestinal distress is

Table 1. Current Therapies Approved for Multiple Myeloma

IMiDs	PIs	Chemotherapy anthracyclines	Chemotherapy alkylators	Steroids	Histone deacetylase inhibitors	mAbs	XPO-1 inhibitor
Thalidomide (po)	Bortezomib (IV/SC)	Doxorubicin (IV)	Cyclophosphamide (IV, po)	Dexamethasone (IV, po)	Panobinostat (po)	Elotuzumab (IV)	Selinexor (po)
Lenalidomide (po)	Carfilzomib (IV)	Liposomal doxorubicin (IV)	Bendamustine (IV)	Prednisone (po)		Daratumumab (IV)	
Pomalidomide (po)	Ixazomib (po)		Melphalan (po, IV)				

Note. IMiD = immunomodulatory drug; PI = proteasome inhibitor; mAB = monoclonal antibody; IV = intravenously; po = orally; SC = subcutaneously.
Information from Chari et al. (2019); National Cancer Institute (2019).

common with this drug but can be better tolerated if patients take dexamethasone in the morning and ixazomib 1 hour before or 2 hours after eating.

With daratumumab, the prevention of adverse events is facilitated by premedication with antipyretics, antihistamines, corticosteroids and postinfusion steroids, antiviral prophylaxis, and monitoring of blood counts. Patients need blood typing in advance of the first dose because daratumumab can interfere with serologic testing; the blood bank should be notified of any patients receiving daratumumab. The main side effect with daratumumab is an infusion-related reaction (which can elicit bronchospasm). Premedication with montelukast prior to dosing (day before) and on the first day of the cycle helps. "Make sure your patient knows the first treatment day is very long, upwards of 10 hours," Ms. Pierre advised.

Subcutaneous dosing of the drug, which will hasten infusion time, is on the horizon, based on the phase III COLUMBA trial showing fewer infusion reactions and no difference in efficacy vs. intravenous delivery (Mateos et al., 2019). With the other monoclonal antibody elotuzumab, clinicians should consider premedication with dexamethasone, antipyretics, and antihistamines; antiviral prophylaxis; infection precautions; and monitoring of blood counts and labs.

NEW REGIMENS ACHIEVE PROMISING OUTCOMES

Newer regimens have combined the lenalidomide/dexamethasone backbone with carfilzomib, ixazomib, daratumumab, and elotuzumab, and achieved high response rates (80% to 90%) and deep, durable responses (Table 2). "This is amazing in the relapsed/refractory setting," Ms. Pierre noted. "We're seeing very long progression-free survival times (20 to 44 months) and overall survivals, with medians that have not even been reached in some studies."

Similarly, with proteasome inhibitor–based therapies (including pomalidomide), overall response rates are very high, and patients are achieving complete and very good partial responses, representing more than a 90% reduction in monoclonal burden. Progression-free survival times are 1 year and longer, and median survival times have not been reached (Table 3).

ALTERNATIVE APPROACHES

A number of alternatives to standard treatments can serve as a bridge to a clinical trial, chimeric antigen receptor (CAR) T-cell therapy, or transplant, Dr. Richter said. One of these is the alkylator bendamustine, which he called "a good tool in your toolbox for patients who have had standard treatments." Other options include the chemotherapy regimens DCEP (a 96-hour continuous infusion of dexamethasone, cyclophosphamide, etoposide, cisplatin), DT-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide with or without thalidomide) and VDT-PACE (with bortezomib). Another good late-line option is the histone deacetylase (HDAC) inhibitor panobinostat, which synergizes well with many myeloma drugs.

Table 2. Phase III Lenalidomide-Based Therapy for Relapsed/Refractory Multiple Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, mo	Median OS, mo	Median f/u (OS), mo
ASPIRE: KRd vs. Rd	87 vs. 67	32 vs. 9	70 vs. 40	26.3 vs. 16.6; HR: 0.69	48.3 vs. 40.4; HR: 0.79	67.0
TOURMALINE-MM1: IxaRd vs. Rd	78 vs. 72	14 vs. 7	48 vs. 39	20.6 vs. 14.7; HR: 0.74	NR	23.0
POLLUX: DRd vs. Rd	93 vs. 76	57 vs. 23	80 vs. 49	44.5 vs. 17.5; HR: 0.44	NR; HR: 0.63	36.0
ELOQUENT-2: ERd vs. Rd	79 vs. 66	5 vs. 9	36 vs. 30	19.4 vs. 14.9; HR: 0.73	48.3 vs. 39.6; HR: 0.78	60.5

Note. ORR = overall response rate; CR = complete response; VGPR = very good partial response; PFS = progression-free survival; OS = overall survival; DRd = daratumumab, lenalidomide, and dexamethasone; ERd = elotuzumab, lenalidomide, and dexamethasone; f/u = follow-up; HR = hazard ratio; IxaRd = ixazomib, lenalidomide, and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; NR = not reported; VGPR = very good partial response. Information from Bahlis et al. (2018); Dimopoulos et al. (2016b, 2017a, 2017b); Lonial et al. (2018); Moreau et al. (2016); Stewart et al. (2017).

Table 3. Phase III Proteasome Inhibitor–Based Therapy for Relapsed/Refractory Multiple Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, mo	Median OS, mo	Median f/u (OS), mo
ENDEAVOR: Kd vs. Vd	77 vs. 63	13 vs. 6	54 vs. 29	18.7 vs. 9.4; HR: 0.53	NR vs. 24.3; HR: 0.79	12.5
CASTOR: DVd vs. Vd	84 vs. 63	29 vs. 10	62 vs. 29	16.7 vs. 7.1; HR: 0.31	NR; HR: 0.63	19.4
PANORAMA-1: PanoVd vs. Vd	61 vs. 55	11 vs. 6	28 vs. 16	12.0 vs. 8.1; HR: 0.63	40 vs. 36; HR: 0.94	–
Elotuzumab (phase II): EVd vs. Vd	66 vs. 63	4 vs. 4	36 vs. 27	9.7 vs. 6.9; HR: 0.72	NR; HR: 0.61	16.0
MMY1001 (phase I): DKd vs. Kd	84	27	71	NR (1-yr PFS: 71%)	NR (1-yr OS: 82%)	12.0

Note. DKd = daratumumab, carfilzomib, and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; EVd = elotuzumab, bortezomib, and dexamethasone; Kd = carfilzomib and dexamethasone; PanoVd = panobinostat, bortezomib, and dexamethasone. Information from Chari et al. (2018a); Dimopoulos et al. (2016a); Jakubowiak et al. (2016); Lentzsch et al. (2017); Palumbo et al. (2016); San-Miguel et al. (2014, 2015).

The newest alternative, which is eliciting much excitement, is selinexor, a first-in-class oral selective inhibitor of nuclear export. "Selinexor has the potential to become the next checkpoint inhibitor in cancer because it works in many different malignancies and will have far-reaching ramifications," he said.

In the pivotal STORM trial of penta-refractory patients, selinexor plus dexamethasone was effective even in patients with prior CAR T-cell therapy (Chari et al., 2018b). With selinexor as part of triplets, Dr. Richter and colleagues have observed response rates exceeding 60%, and median progression-free survival times of 9 months; even better outcomes have been observed with selinexor paired with daratumumab. As quadruplets become more common as upfront therapy, and these patients progress, "you have to start considering drugs like selinexor," he said. The STOMP basket trial is evaluating various combination regimens involving this exciting new drug.

WHICH DRUGS FOR WHICH PATIENTS?

With many beneficial agents available, clinicians are tasked with selecting the best drug or combination for an individual RRMM patient, and best sequence of treatments as that patient progresses. According to Ms. Pierre, this means taking into account the timing of therapy, response to prior therapy, aggressiveness of relapse, and performance status. Shared decision-making between the patient and health-care team is important and involves "listening to your patient's preferences and goals, considering the agents that are approved for their situation and disease trajectory, and realizing what's appropriate for them, given their needs and their disease," she said. In general, within the limits of a risk-adapted model, triplets are preferred over doublets, and quadruplets sometimes have a role.

EMERGING THERAPIES IN CLINICAL TRIALS

Enrollment on a clinical trial is always the preferred option, especially in earlier-stage disease, where many novel agents are being tested. "The field is extremely crowded, with many drugs in the pipeline, so we're really hopeful about the future and therapies we will have," Dr. Richter said, who elaborated on some of the agents in these trials.

Similar to CAR T-cell products but easier to produce are the "off the shelf" BiTE (bispecific T-cell engager) antibodies, i.e., "bifunctionals." One generating much interest is the CD38/CD3-targeting drug GBR 1342, which in preclinical models appears more active than daratumumab. The next-generation IMiD CELMoD CC-220, or iberdomide, "is probably the most active IMiD out there," he said. "It will be a backbone therapy and a mainstay of treatment in the future."

A novel therapeutic likely to be approved within 1 year is venetoclax (which is already approved in acute myeloid leukemia and lymphoma). Venetoclax inhibits BCL-2, an antiapoptotic protein. It

synergizes well with carfilzomib, which indirectly inhibits another antiapoptotic protein, MCL-1, "together producing amazing responses." Venetoclax works in two types of myeloma patients: those with (11;14) translocations and those who are high expressers of BCL-2. In these subsets, responses appear to be rapid and durable and remissions are durable. "When the dominant clone is 11;14, we should bring venetoclax in," he recommended.

Dr. Richter said he is also excited to see the emergence of antibody-drug conjugates (ADCs). One targeting B-cell maturation antigen (BCMA), an antigen expressed on all myeloma cells, is belantamab. Belantamab is likely to be approved in 2020 and will "usher in a new realm of treatment" because it is an off-the-shelf product that often produces "amazing responses," he noted. "We can't wait to get this drug in the clinic."

Another new approach in RRMM is mutation-driven therapy, which is being tested in the MyDRUG study. MyDRUG is enrolling high-risk patients who undergo gene sequencing then are treated with ixazomib/pomalidomide/lenalidomide/dexamethasone plus a drug that addresses the identified driver of their disease (for example, *BRAF* mutation). "Here, we are really giving personalized therapy. When we have this type of evaluation, we can start thinking outside the box," he continued.

Trials are also evaluating next-generation CD38 drugs—TAK-079 and SAR442085—and drugs hitting novel targets, including Onc201, AMG 397, and BETi. Additionally, the lipophilic peptide-conjugated alkylator melflufen, which is essentially a monthly infusion of a version of melphalan, could prove useful in penta-refractory patients.

Focus on CAR T-Cell Therapy

CAR T-cell therapy is expected to be approved for myeloma next year, mostly likely bb2121. After treatment with bb2121, median progression-free survival is almost 1 year for all-comers, but increases to almost 18 months in patients achieving minimal residual disease (MRD)-negative status (Raje et al., 2018). These are impressive outcomes among patients with a median of 7 prior lines of therapy, whose expected overall survival would cap around 3 months.

Advanced practitioners need to recognize and know how to deal with post-infusion cytokine release syndrome (CRS), although most are low grade and easily managed. The drugs in the toolbox for CRS are the anti-interleukin (IL)-6 agents tocilizumab and siltuximab, the anti-IL-1 agent anakinra, along with steroids (especially when the aforementioned drugs are not effective and/or there is neurotoxicity). Post CAR T-cell therapy, patients should be monitored and treated for prolonged cytopenia and infections (including cytomegalovirus). ●

Disclosure

Ms. Pierre has consulted for Celgene and served on the advisory boards of Amgen and Karyopharm. Dr. Richter has served on the speakers bureaus of Celgene and Janssen, and served as a consultant or advisor for Amgen, BMS/Pfizer, Celgene, Janssen, Karyopharm, Oncopeptides, Sanofi, and Takeda. This symposium was sponsored by educational grants from Celgene Corporation, Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC., and Oncopeptides, Inc.

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