Health Monitor®

Clinician Update

Multiple Myeloma

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How advances in MM are **changing the treatment paradigm**

In the past decade, major changes have occurred in the response criteria and treatment for relapsing multiple myeloma (MM). As the treatment of MM has advanced, so too has the molecular characterization of disease, which has expanded the definition of high-risk features beyond those used in the revised International Staging System (see box on p. 4).[1]

There has been a revolution in therapies for relapsed MM, says Joseph Mikhael, MD, Chief Medical Officer of the International Myeloma Foundation. "The first wave of this movement was in a series of phase 3 trials that explored multiple triplet combinations to provide deeper and more durable responses than had been seen before in relapsed myeloma," he says. "Those trials resulted in multiple options for therapies combining agents from the three main classes of proteasome inhibitors, immunomodulatory agents and monoclonal antibodies. This is a critically important development, as high-risk MM is associated with worse progression-free and overall survival outcomes."

More options to consider after first relapse

While it is generally agreed that more intensive therapy is warranted for patients with high-risk disease, appropriate positioning of different therapeutic options—in both the first-line and early relapse settings—remains unclear.[2-4] "Among many different standard of care options, we currently lack randomized control trial data on best choice second-line therapy in relapsed/refractory multiple myeloma, including standard and especially high-risk patients," says Muhamed Baljevic, MD, an Associate Professor of Medicine and Director of Plasma Cell Disorders Research and Vanderbilt Amyloidosis Multidisciplinary Programs (VAMP) at Vanderbilt University Medical Center in Nashville.

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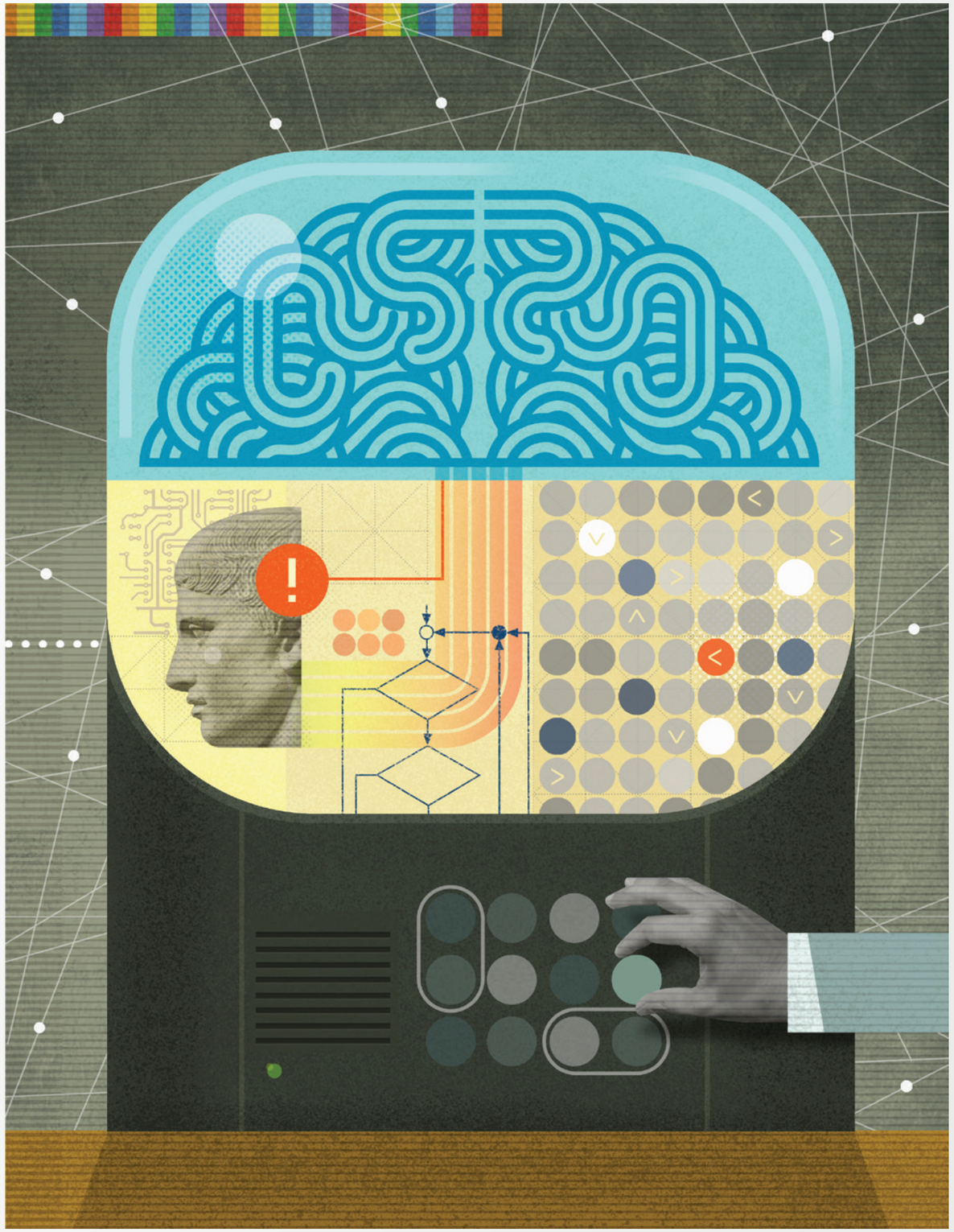

Illustration by Gordon Studer

"Our understanding of outcomes in these patients comes mainly from subgroup analyses of major trials in patients who harbor high-risk features," Dr. Baljevic says. Significant therapeutic advances include the following:

Anti-CD38 monoclonal antibodies (mAbs). "Introduction of anti-CD38 mAbs in the MM armamentarium represents one of the major advances that led to improvement of long-term outcomes for both newly diagnosed and relapsing MM," says Dr. Baljevic. "Generally speaking, early incorporation of anti-CD38 mAb therapy, particularly for high-risk MM patients, is a preferred choice. While clinical trials do not have comparative head-to-head data for clear understanding if one drug may be better than the other, they all conclusively demonstrated the benefit of anti-CD38 mAb-containing triplets versus corresponding doublet therapies," Dr. Baljevic says. Indeed, numerous clinical trials back this assertion.[5-11] "Quadruplet treatments also are promising in newly diagnosed frontline settings as well as after first relapse."

Early on, it is advisable to try to avoid repeat exposures to agents that patients may already be refractory to considering the variety of available drugs within the same or different classes, Dr. Baljevic notes. "It is essential to establish careful understanding of prior drug exposures versus refractoriness status for all treatment classes, as careful decision-making and choice of subsequent therapies needs to be tailored based on these characteristics, particularly with respect to anti-CD38 mAb therapy," he says.

CAR T-cell and bispecific antibody therapies. Dr. Baljevic notes that some physicians (and patients) may prefer to "upgrade" to newer generations of therapies or, increasingly, explore new options with novel mechanisms of action. "The explosion of CAR T-cell and bispecific antibody therapies in relapsing multiple myeloma and their continued studying in earlier lines will undoubtedly shape our field for years to come," he says.

Two different CAR T-cell therapies have been approved in myeloma, both of which target the B-cell maturation antigen (BCMA) on the surface of the myeloma cell.[12,13] "These therapies tripled the response rate of traditional late-stage myeloma therapies, with response rates in the 75% to 98% range," says Dr. Mikhael. "These deep and durable responses also have the advantage of CAR T-cell therapy being a 'one and done' approach, as we do not routinely give maintenance therapy after T cells are reinfused."

In addition, there are three bispecific antibodies approved for relapsed MM, two that target BCMA and one that targets the novel GPRC5D antigen on the myeloma cell.[13,14] "These therapies have a response rate of approximately 63% to 75%, at least doubling the rate of prior therapies, with the exception of CAR T," he says. Although they do require ongoing therapy, they have the advantage of not requiring T-cell collection from patients as with CAR T-cell therapy.

Focus on patient goals and inclusivity

When selecting therapy at first relapse, Dr. Baljevic says it is important to consider not only disease features and treatment history, but also patients' unique needs. "Patient preferences and goals of care, as well as logistics of drug administration (route and frequency of administration) and treatment costs play a significant role in the ultimate decision-making process," he says. "Patients who are part of underserved communities or demographics can be at a particular disadvantage when it comes to treatment access and subsequent long-term outcomes."

For that reason, Dr. Baljevic says it is also important to discuss clinical trials as an option. "Consideration of clinical trials is always appropriate, especially for high-risk patients, in every phase of disease, from newly diagnosed to highly relapsed/refractory MM," he notes. "It remains our goal to ensure clinical trials are as representative as possible of different demographic populations, so that data generated can be as broadly applicable as possible. Patients belonging to underserved populations are particularly vulnerable and deserve equal access to care."

A bright future

As research continues, stem cell transplantation will likely be less important in the future due to better drug combinations and newer immunotherapies being used in earlier lines of therapy—a development that was inconceivable a few years ago. "In 25 years of myeloma care and research, I do not think there has been a more exciting time than the present for patients," says Dr. Mikhael. "In all areas of myeloma care, we have outstanding research ongoing to help patients live better and live longer—and eventually, live life without myeloma as we seek a cure."

—by Morgan Meissner

Factors that define high-risk disease

"High-risk MM can be defined in several different ways, most commonly by the presence of high-risk cytogenetic features," explains Muhamed Baljevic, MD, an Associate Professor of Medicine and Director of Plasma Cell Disorders Research and Vanderbilt Amyloidosis Multidisciplinary Programs (VAMP) at Vanderbilt University Medical Center in Nashville. High-risk MM is defined by the presence of one or more of the following:

- High-risk cytogenetic features, such as t(4;14), t(14;16), t(14;20), gain 1q, del(17p), or p53 mutation.[2,3] Patients who have two or more high-risk cytogenetics are classified as having ultra-high-risk disease.
- Disease characteristics, including extramedullary disease, circulating plasma cells (or secondary plasma cell leukemia at relapse) and early relapse, defined as occurring within 24 months from the start of induction therapy.[1-4]
- Refractoriness to prior therapies. "Prognostic markers that influence outcomes in patients with MM relapse also include patient performance status, as well as refractoriness to major anti-MM drug classes (proteasome inhibitors, immunomodulatory drugs, anti-CD38 antibodies) at the time of relapse," Dr. Baljevic says. "Triple-class or particularly penta-class refractory patients are well described for having poor long-term overall outcomes compared with those patients who are less refractory."
- Patient-specific characteristics. "General considerations, such as frailty, underlying significant comorbid conditions (e.g., renal impairment) as well as residual toxicities from prior therapies, can all impact how well patients with relapsed or refractory disease can tolerate subsequent therapies," Dr. Baljevic notes.

References

1. Hagen P, et al. High-risk disease in newly diagnosed multiple myeloma: beyond the R-ISS and IMWG definitions. *Blood Cancer J.* May 30 2022;12(5):83.
2. Costa LJ, et al. Defining and managing high-risk multiple myeloma: current concepts. *J National Compr Canc Network.* Dec 2020;18(12):1730-1737.
3. Marcon C, et al. Expert consensus on the definition and management of high risk multiple myeloma. *Front Oncol.* 2022;12:1096852.
4. National Comprehensive Cancer Network. NCCN guidelines: multiple myeloma, version 4.2023. Updated August 25, 2023.
5. Dimopoulos M, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma: results from a randomised, multicentre, open-label, phase 3 study. *Lancet.* Jul 18 2020;396(10245):186-197.
6. Moreau P, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet.* Jun 19 2021;397(10292):2361-2371.
7. Attal M, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet.* Dec 7 2019;394(10214):2096-2107.
8. Dimopoulos MA, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma: an open-label, randomised, phase 3 trial. *Lancet Oncol.* Jun 2021;22(6):801-812.
9. Landgren O, et al. Subgroup analysis based on cytogenetic risk in patients with relapsed or refractory multiple myeloma in the CANDOR study. *Br J Haematol.* Sep 2022;198(6):988-993.
10. Spicka I, Moreau P, Martin TG, et al. Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis. *Eur J Haematol.* Nov 2022;109(5):504-512.
11. Martin T, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. *Blood Cancer J.* May 9 2023;13(1):72.
12. Sheykhhasan M, et al. CAR T therapies in multiple myeloma: unleashing the future. *Cancer Gene Ther.* 2024;31:667-686.
13. Cohen A. CAR T cells and bispecific antibodies: new options in multiple myeloma. *Targeted Oncology.* March 8, 2024. Available at *targetedonc.com.*
14. Swan D, et al. Bispecific antibodies in multiple myeloma: Opportunities to enhance efficacy and improve safety. *Cancer.* 2023 Mar; 15(6):1819.

PRACTICE PEARLS

ADJUNCTIVE THERAPIES to manage complications and side effects

The nature of MM and its treatment can lead to other health problems. Here are strategies to help control common sequelae.

Managing multiple myeloma (MM) encompasses not only the use of myeloma-directed therapies but also the incorporation of adjunctive treatments. Many organ systems are affected by MM, and the effects of the disease on the body can create a variety of bothersome symptoms and potentially dangerous complications. Additionally, as patients with MM are exposed to a growing number of lines of treatment—and for longer durations with maintenance therapy regimens—management increasingly requires physicians to address various side effects.

"It's important to educate patients and set realistic expectations," says Carol Ann Huff, MD, Medical Director for the Johns Hopkins Kimmel Cancer Center. "Then offer support and adjustment as needed." Here are some of the most common symptoms, complications and side effects, as well as how to address them.

Bone damage

This complication of MM is caused by the destruction and crowding out of healthy bone marrow cells by myeloma cells. As a result, bone pain is among the most common presenting symptoms of myeloma, and more than 80% of patients will develop bone complications over the course of disease.[1] These include bone fracture, as well as hypercalcemia and spinal cord compression.

In addition, certain anticancer therapies, such as steroids, can lead to weakening of the bones and may contribute to progression of bone disease.[2] Patients also may have comorbid conditions that place them at risk for poor bone health, including osteoporosis, metastatic malignancies, immobility and side effects from long-term steroid and other drug use. Plus, certain factors can contribute to osteoporosis, such as renal disease and hormonal changes.

Management of bone disease typically includes the use of bisphosphonates (e.g., zoledronic acid and pamidronate) and RANK-L inhibitors (e.g., denosumab). While these drugs can help slow and even reverse the progression of

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Illustration by Stuart Kinlough / Ikon Images

bone disease, they can lead to osteonecrosis, most notably osteonecrosis of the jaw (ONJ), a rare but serious side effect that may occur with prolonged use of bisphosphonates.[2]

Risk for ONJ can be mitigated by reducing the frequency of treatment and by avoiding invasive jaw procedures such as dental extractions and implants during treatment. All other dental procedures, including regular cleanings, fillings, root canals and crowns, should be performed as needed. Patients should be instructed to inform their dentist that they are receiving bisphosphonates or RANK-L inhibitors and encouraged to seek a second opinion from a dental specialist before receiving invasive dental procedures.

Pain medications such as narcotics may also be used to help manage bone pain. However, because MM can compromise the health of the kidneys, avoidance of nonsteroidal anti-inflammatory drugs is generally recommended.[3] In cases of severe bone disease, surgery may be needed to address fractures and other complications.

Neuropathy

Certain treatments can lead to nerve damage and peripheral neuropathy, which causes numbness, tingling or pain in the extremities. "Neuropathy can be problematic as there are not available therapies to treat this, only medications that may lessen the intensity of neuropathy symptoms," says Dr. Huff. "Early intervention and prevention, where possible, are the best approaches."

Neuropathy has been identified as a potential side effect of the immunomodulatory drug (IMiD) thalidomide as well as the proteasome inhibitors bortezomib and ixazomib.[3] The risk for peripheral neuropathy with bortezomib can be reduced by using subcutaneous forms and weekly dosing. If peripheral neuropathy occurs, Dr. Huff suggests early intervention with dose reductions if possible. She also recommends careful questioning to identify early symptoms that may warrant dose adjustment or intervention.

"Some have found supplements helpful to lessen neuropathy, although clinical trials are lacking," she notes. These include coenzyme Q10, B vitamins and alpha lipoic acid. "Neuropathy that is painful is also sometimes helped with gabapentin, pregabalin or duloxetine."

Blood effects

A variety of blood effects can be observed as a result of both MM and treatment, including anemia, thrombocytopenia and neutropenia, as well as thromboembolic disease. These effects can lead to other–potentially serious–complications as well, including bleeding, infection and fatigue. In addition, neutropenia and other blood effects are seen in patients treated with anti-CD38 monoclonal antibody-based regimens, IMiDs (lenalidomide and pomalidomide), proteasome inhibitors (bortezomib) and the nuclear export inhibitor selinexor. When patients are receiving IMiDs such as thalidomide, lenalidomide or pomalidomide, additional medications, including low molecular weight heparin, warfarin or one of the newer direct anticoagulants, are often added to reduce the risk of blood clots.[3,4]

Blood effects may be managed with dietary supplements (e.g., iron for anemia) as well as colony-stimulating factors. Preventive measures, including vaccinations, antibiotics, antivirals and–depending on the treatment regimen–antifungals and intravenous antibodies, may be administered to reduce the risk of infection due to neutropenia.

Gastrointestinal effects

A variety of MM treatments can cause gastrointestinal problems such as constipation, diarrhea, nausea and vomiting.[2,3] Dr. Huff notes that diarrhea is particularly a problem with long-term lenalidomide treatment. "For lenalidomide-associated diarrhea, use of bile acid-binding resins can help," she says. "Cholestyramine or colesevelam are often more helpful than OTC antidiarrheals."

Dr. Huff notes that constipation can also occur with steroid use, as well as with the use of antiemetics such as ondansetron and certain pain medications. Stool softeners or laxatives can help relieve constipation, as well as a high-fiber diet, increased water intake and gentle exercise.

Sleep disturbances

Sleep problems such as insomnia are a common side effect associated with steroid use. Changes in sleeping patterns can also be indicative of nervous system effects associated with bispecific antibody therapies.[2]

"Sleep disturbances can be mitigated in some by changing the time of day of steroid administration, using sleeping medications, and with dose reductions of steroids where necessary," says Dr. Huff. For example, she says, "Sometimes nighttime dosing helps as patients sleep through the first 6 to 8 hours." She cautions that this approach will not work for all patients, though, and may not be possible depending on the requirements of treatment. At times, steroid dose reductions where medically appropriate may be needed. Melatonin or other sleep aids are of variable help.

Novel drug side effects

Chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies represent new classes of drugs that have revolutionized MM treatment, particularly in later stages of disease. However, with these has come a new set of rare but potentially serious side effects, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[2,3] Use of these drugs requires prolonged monitoring to support early detection and rapid initiation of treatment within specialized centers.

–by Morgan Meissner

References

1. **Bernstein ZS, et al. Bone disease in multiple myeloma: biologic and clinical implications. *Cells*. Jul 27 2022;11(15).**
2. **American Cancer Society. Drug therapy for multiple myeloma. Updated August 15, 2023. Available at *cancer.org*.**
3. **The Multiple Myeloma Research Foundation. Treatments for multiple myeloma. Available at *themmrf.org*.**
4. **Mikulaki D, et al. Risk factors of infection in relapsed/refractory multiple myeloma patients treated with lenalidomide and dexamethasone (RD) regimen: real-life results of a large single-center study. *J Clin Med*. 2022 Oct;11(19):5908.**

NONDRUG INTERVENTIONS FOR **MANAGING MYELOMA SYMPTOMS**

In addition to adjunctive medical treatments, it's important to discuss nondrug therapies with patients, notes Shebli Atrash, MD, Assistant Professor of Clinical Medicine, Wake Forest Medical College, and multiple myeloma specialist at Atrium Health Levine Cancer Institute, Charlotte, NC. "Complementary and supportive therapies can significantly manage symptoms and improve the quality of life for individuals with multiple myeloma," he says. Here, Dr. Atrash discusses some of the nondrug interventions that can help.

Q. What types of exercise do you recommend to patients and why?

A. Many myeloma therapies increase the risk of blood clots. Therefore, physical activity and exercise are advisable. Walking is the preferred physical activity because running or lifting weights could cause fractures in weak bones. Other good options include a stationary bike with low level of resistance or an elliptical machine. In general, there should be more focus on light exercises. I tell my patients, "The more you do, the better, but if you have muscle soreness the next day it means you overdid it."

Q. Which complementary therapies might be helpful?

A. There are several options, but I'll point out two of them. First, acupuncture appears to be promising and is currently undergoing investigation to explore its capabilities in the treatment of peripheral neuropathy, nausea and fatigue. Another thing that can help patients overall: engaging in creative activities to reduce stress. These activities—for example, journal writing, taking an art class or doing photography—can offer a sense of accomplishment and distraction from symptoms.

Q. What psychosocial interventions do you recommend?

A. The available support groups for multiple myeloma are exceptional because of the strength of support that families and friends have created. These can provide emotional support, a sense of community and a venue to share experiences and coping strategies. Patients can find them through the International Myeloma Foundation (*myeloma.org*), the Leukemia & Lymphoma Society (*lls.org*) and similar organizations.

Q. Are there any simple, everyday strategies that patients may find helpful?

A. Yes, and one of the most important is hydration. Myeloma progression is often complicated with dehydration symptoms. Staying hydrated can help manage symptoms such as fatigue and constipation and help protect the kidneys from myeloma injury.

In addition, muscle cramps remain a problem for patients on chemotherapy. Swallowing a teaspoon of mustard or an ounce of pickle juice might help decrease muscle cramps, as reported anecdotally by patients. It has not been determined why these may help. Some research speculates it could be because they contain acetic acid, which the body uses to produce acetylcholine, an essential neurotransmitter for leg muscle contractions. Yellow mustard is the only kind of mustard documented to relieve nighttime leg cramps, although more research is needed to confirm this.

MANAGING THE PAIN AND FATIGUE of multiple myeloma

Those run-down feelings that come with MM can feel overwhelming to patients. Here, strategies that may help improve their quality of life.

Adjusting to the idea that you must face down a form of chronic blood cancer for the rest of your life is hard enough, and then there's dealing with the daily reality—namely, the pain and fatigue that dog the days of many with multiple myeloma (MM), according to a survey in the *Annals of Hematology*.[1] Understanding why they are reported so often is complex. "It's partially related to the disease itself," explains Kate Campion, DNP, AGACNP, a nurse practitioner in heme malignancies specializing in MM at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital. After all, MM is a cancer of plasma cells in the bone marrow, which can impact not only the bones (giving them a moth-eaten appearance), but also organs like the kidneys. It can also lead to lytic lesions (i.e., the loss of pockets of bone), fractures, and spinal cord compression, all of which contribute to discomfort and exhaustion.

Plus, Campion points out that other factors, including anemia and side effects of the drugs used to treat the disease, can contribute to making a patient feel run down. Not to be underestimated is the psychological element—there is good evidence that both pain and fatigue are linked to global distress as well as depression in patients with MM, according to research in 2020 in *Cancer Nursing*.[2]

The encouraging news is that a multipronged care approach to easing discomfort, decreasing stress, and boosting energy can be a boon to MM patients. And while pain medication like acetaminophen (for patients on blood thinners) and gabapentin (for nerve pain) may be a help, other lifestyle and psychosocial strategies may also improve outcomes.

Continued on p. 18 ►

Illustration by Jeannie Phan

For your adult patients with relapsed or refractory multiple myeloma

~42 MONTHS

UNPRECEDENTED mPFS WITH SARCLISA + Kd

LONGEST EVER REPORTED

in a phase 3 trial that included lenalidomide-refractory patients[1-6*]

*Based on a review of published phase 3 trials that included lenalidomide-refractory patients with RRMM. Interpret with caution, as various factors, including patient population, differ between trials.

SARCLISA + Kd
IKEMA

Final analysis: mPFS 41.7 months with SARCLISA + Kd (n=179) vs 20.8 months with Kd alone (n=123), **HR=0.59** (95% CI: 0.42, 0.83) at a median follow-up of 44 months[2]

Interim analysis: mPFS NR with SARCLISA + Kd vs 20.27 months with Kd alone, HR=0.548 (95% CI: 0.37, 0.82; *P*=0.0032) at a median follow-up of 20.7 months[1]

IKEMA study design (SARCLISA + Kd): A multicenter, multinational, randomized, open-label, 2-arm, phase 3 study evaluated the efficacy and safety of SARCLISA in 302 patients with RRMM who had received 1 to 3 prior therapies. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Kd (n=179) or Kd alone (n=123), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. PFS was the primary endpoint; ORR, ≥VGPR, CR, MRD-, and OS were key secondary endpoints.[1,7]

PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. An interim analysis was conducted when 65% of the 159 PFS events (ie, 103 events) were observed. *P* value is not reported as this is a non-inferential analysis of the primary endpoint that was met at the time of the interim analysis.[1,7]

Indication

SARCLISA (isatuximab-irfc) is indicated:

- In combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy

Important Safety Information

CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in clinical trials of SARCLISA in relapsed or refractory multiple myeloma (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

Neutropenia

SARCLISA may cause neutropenia.

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

Monitor complete blood cell counts periodically during treatment. Consider the use of antibacterial and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 4.1%.

In the ongoing IKEMA study, at a median follow-up time of 21 months, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

The most common (≥1%) second primary malignancies in clinical trials of SARCLISA in relapsed or refractory multiple myeloma (N=329) included skin cancers (5% with SARCLISA-containing regimens and 2.6% with comparative regimens) and solid tumors other than skin cancer (3% with SARCLISA-containing regimens and 1.8% with comparative regimens). All patients with non-melanoma skin cancer continued treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

1L=first line; 2L=second line; ASCT=autologous stem cell transplant; CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; IV=intravenous; Kd=carfilzomib and dexamethasone; M-protein=monoclonal protein; mPFS=median progression-free survival; MRD-=minimal (or measurable) residual disease negativity; mSMART=Mayo Clinic Stratification for Myeloma and Risk-adapted Therapy; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RRMM=relapsed or refractory multiple myeloma; VGPR=very good partial response; VR=bortezomib and lenalidomide; VRd=bortezomib, lenalidomide, dexamethasone.

SARCLISA + Kd Was Studied in Patients Like Alice[1]

68 years of age

Hypothetical patient case.

Alice's patient information	Proportion of patients in IKEMA
1 prior line of therapy • 1L: VRd induction → ASCT → VR maintenance • VGPR for 13 months posttransplant	44%
Refractory to lenalidomide • Rapid, aggressive disease progression on lenalidomide maintenance	33%
Positive for 1q21+ • Defined as high risk by the National Comprehensive Cancer Network (NCCN®), IMWG, and mSMART guidelines[8-10]	42%

Consider SARCLISA + Kd for your patients with RRMM who have high-risk factors like Alice.[1]
See her full patient profile at sarclisahcp.com

Important Safety Information (cont'd)

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false-positive indirect antiglobulin test (indirect Coombs test). The indirect antiglobulin test was positive during Isa-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment.

Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and that SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients receiving Isa-Kd were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

USE IN SPECIAL POPULATIONS

Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see Brief Summary of full Prescribing Information on the following pages.

References: 1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Martin T, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized phase 3 study. *Blood Cancer J*. 2023;13:72. doi:10.1038/s41408-023-00797-8 **3.** Hernández-Rivas JA, Ríos-Tamayo R, Encinas C, Lahuerta JJ. The changing landscape of relapsed and/or refractory multiple myeloma (MM): fundamentals and controversies. *Biomarker Res*. 2022;10(1):1-23. **4.** Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol*. 2022;23:65-76. **5.** Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25(25):3892-3901. **6.** Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N Engl J Med*. 2023;388(11):1002-1014. doi:10.1056/NEJMoa2213614 **7.** Data on file. sanofi-aventis U.S. LLC. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.3.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed December 19, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **9.** Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962. **10.** Mayo Clinic. Treatment of relapsed myeloma. Accessed January 17, 2023. https://www.msmart.org/mm-treatment-guidelines

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MAT-US-2307253-v2.0-12/2023

SARCLISA®
(isatuximab-irfc)
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

SARCLISA® **Rx Only**
(isatuximab-irfc) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

SARCLISA is indicated:

- in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Administer pre-infusion medications *[see Dosage and Administration (2.2)]*.
- SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur *[see Warnings and Precautions (5.1)]*.

The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone, according to the schedule in Table 1 *[see Clinical Studies (14) in the full prescribing information]*.

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carfilzomib and Dexamethasone

Cycle	Dosing schedule
Cycle 1	Days 1, 8, 15, and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

SARCLISA is used in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone. For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies (14) in the full prescribing information and manufacturer's prescribing information.

Missed SARCLISA Doses

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.2 Recommended Premedications and Antiviral Prophylaxis

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions *[see Warnings and Precautions (5.1)]*:

- When administered in combination with SARCLISA and pomalidomide: Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age). When administered in combination with SARCLISA and carfilzomib: Dexamethasone 20 mg (intravenously on the days of SARCLISA and/or carfilzomib infusions, orally on day 22 in cycle 2 and beyond, and orally on day 23 in all cycles).
- Acetaminophen 650 mg to 1,000 mg orally (or equivalent).
- H2 antagonists
- Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the dose to be administered before infusion as part of the premedication and part of the backbone treatment. Administer dexamethasone before SARCLISA and pomalidomide and before SARCLISA and carfilzomib administration.

Administer the recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion.

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation based on standard guidelines *[see Adverse Reactions (6.1)]*.

2.3 Dose Modifications

No dose reduction of SARCLISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematological toxicity *[see Warnings and Precautions (5.2, 5.4)]*. For information concerning drugs given in combination with SARCLISA, see manufacturer's prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows:

Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) *[see Dosage and Administration (2.1)]*. More than one SARCLISA vial may be necessary to obtain the required dose for the patient.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection from the vial and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see Table 2). Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C to 8°C, followed by 8 hours (including the infusion time) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.
- On the days where both SARCLISA and carfilzomib are administered, administer dexamethasone first, followed by SARCLISA infusion, then followed by carfilzomib infusion.

Infusion Rates

Following dilution, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only in the absence of infusion-related reactions *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Table 2: Infusion Rates of SARCLISA Administration

	Dilution Volume	Initial Rate	Absence of Infusion-Related Reaction	Rate Increment	Maximum Rate
First infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/hour	200 mL/hour
Subsequent infusions	250 mL	200 mL/hour	–	–	200 mL/hour

4 CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Serious infusion-related reactions including life-threatening anaphylactic reactions have occurred with SARCLISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, infusion-related reactions occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) *[see Adverse Reactions (6.1)]*. All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes *[see Adverse Reactions (6.1)]*.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients.

To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent, and dexamethasone *[see Dosage and Administration (2.2)]*.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 *[see Dosage and Administration (2.5)]*. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) infusion-related reaction occurs and institute appropriate management.

5.2 Neutropenia

SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%) *[see Adverse Reactions (6.1)]*.

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3–4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%) *[see Adverse Reactions (6.1)]*.

Monitor complete blood cell counts periodically during treatment. Consider the use of antibacterial and antiviral prophylaxis during treatment *[see Dosage and Administration (2.2)]*. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia delay SARCLISA dose until neutrophil count recovery to at least 1 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

5.3 Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 4.1%.

In ICARIA-MM, at a median follow-up time of 52 months, second primary malignancies occurred in 7% of patients in the Isa-Pd arm and in 2% of patients in the Pd arm.

In ongoing IKEMA study, at a median follow-up time of 21 months, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (5% with SARCLISA-containing regimens and 2.6% with comparative regimens) and solid tumors other than skin cancer (3% with SARCLISA-containing regimens and 1.8% with comparative regimens). All patients with non-melanoma skin cancer continued treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

5.4 Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). The indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment.

Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices *[see Drug Interactions (7.1)]*.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein *[see Drug Interactions (7.1)]*.

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Multiple Myeloma

Combination treatment with pomalidomide and dexamethasone (Isa-Pd)

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and dexamethasone (Isa-Pd) (n=152) or pomalidomide and dexamethasone (Pd) (n=149) *[see Clinical Studies (14) in the full prescribing information]*. Among patients receiving Isa-Pd, 66% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

Permanent treatment discontinuation due to an adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). SARCLISA alone was discontinued in 3% of patients due to infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea.

Table 3 summarizes the adverse reactions in ICARIA-MM.

Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

Adverse Reactions	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
General disorders and administration site conditions						
Infusion-related reaction*	38	1.3	1.3	0	0	0
Infections						
Upper respiratory tract infection†	57	9	0	42	3.4	0
Pneumonia‡	31	22	3.3	23	16	2.7
Blood and lymphatic system disorders						
Febrile neutropenia	12	11	1.3	2	1.3	0.7
Respiratory, thoracic and mediastinal disorders						
Dyspnea§	17	5	0	12	1.3	0
Gastrointestinal disorders						
Diarrhea	26	2	0	19	0.7	0
Nausea	15	0	0	9	0	0
Vomiting	12	1.3	0	3.4	0	0

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*Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and drug hypersensitivity.

†Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

‡Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenzal, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jirovecii pneumonia.

§Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the hematology laboratory abnormalities in ICARIA-MM.

Table 4: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Pd versus Pd in ICARIA-MM

Laboratory Parameter	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin decreased	99	32	0	97	28	0
Neutrophils decreased	96	24	61	92	38	31
Lymphocytes decreased	92	42	13	92	35	8
Platelets decreased	84	14	16	79	9	15

The denominator used to calculate the percentages was based on the safety population.

Combination treatment with carfilzomib and dexamethasone (Isa-Kd)

The safety of SARCLISA was evaluated in IKEMA, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg intravenously weekly in the first cycle, and every two weeks thereafter, in combination with carfilzomib and dexamethasone (Isa-Kd) (n=177) or carfilzomib and dexamethasone (Kd) (n=122) *[see Clinical Studies (14) in the full prescribing information]*. Among patients receiving Isa-Kd, 68% were exposed to SARCLISA for 12 months or longer and 51% were exposed for greater than 18 months.

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

Permanent treatment discontinuation due to an adverse reaction (grades 1–4) occurred in 8% of patients who received Isa-Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Kd were infections (2.8%). SARCLISA alone was discontinued in 0.6% of patients due to infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 33% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (30%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain.

Table 5 summarizes the adverse reactions in IKEMA.

Table 5: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in IKEMA

Adverse Reactions	SARCLISA + Carfilzomib + Dexamethasone (Isa-Kd) (N=177)			Carfilzomib + Dexamethasone (Kd) (N=122)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
General disorders and administration site conditions						
Infusion-related reaction*	46	0.6	0	3.3	0	0
Fatigue†	42	5	0	32	3.3	0
Infections						
Upper respiratory tract infection‡	67	9	0	57	7	0
Pneumonia§	36	19	3.4	30	15	2.5
Bronchitis¶	24	2.3	0	13	0.8	0
Vascular disorders						
Hypertension#	37	20	0.6	32	18	1.6
Respiratory, thoracic and mediastinal disorders						
Dyspnea Þ	29	5	0	24	0.8	0
Cough ß	23	0	0	15	0	0
Gastrointestinal disorders						
Diarrhea	36	2.8	0	29	2.5	0
Vomiting	15	1.1	0	9	0.8	0

*Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and hypersensitivity.

†Fatigue includes fatigue and asthenia.

‡Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.

§Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis.

¶Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.

#Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.

ÞDyspnea includes dyspnea and dyspnea exertional.

ßCough includes cough, productive cough, and allergic cough.

Table 6 summarizes the hematology laboratory abnormalities in IKEMA.

Table 6: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Kd versus Kd in IKEMA

Laboratory Parameter	SARCLISA + Carfilzomib + Dexamethasone (Isa-Kd) (N=177)			Carfilzomib + Dexamethasone (Kd) (N=122)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin decreased	99	22	0	99	20	0
Lymphocytes decreased	94	52	17	95	43	14
Platelets decreased	94	19	11	88	16	8
Neutrophils decreased	55	18	1.7	43	7	0.8

The denominator used to calculate the percentage was based on the safety population.

Description of Selected Adverse Reactions

Infusion-related reactions

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, grade 2 in 32%, grade 3 in 1.3%, and grade 4 in 1.3% of the patients. Signs and symptoms of grade 3 or 4 infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 30%. The median time to infusion interruption was 55 minutes. SARCLISA was discontinued in 2.6% of patients due to infusion-related reactions.

In IKEMA, infusion-related reactions were reported in 81 patients (46%) treated with Isa-Kd. Grade 1 infusion-related reactions were reported in 14%, grade 2 in 32%, and grade 3 in 0.6% of the patients treated with Isa-Kd. Signs and symptoms of grade 3 infusion-related reactions included dyspnea and hypertension. SARCLISA was discontinued in 0.6% of patients due to infusion-related reactions *[see Warnings and Precautions (5.1)]*.

In a separate study (TCD14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

Infections

In ICARIA-MM, the incidence of grade 3 or higher infections was 43% in the Isa-Pd group. Pneumonia was the most common severe infection with grade 3 reported in 22% of patients in the Isa-Pd group compared to 16% in the Pd group, and grade 4 in 3.3% of patients in the Isa-Pd group compared to 2.7% in the Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in the Isa-Pd group compared to 5% in the Pd group. Fatal infections occurred in 3.3% of patients in the Isa-Pd group and in 4% in the Pd group.

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 3.4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.8% of patients in the Isa-Kd group compared to 4.9% in the Kd group. Fatal infections occurred in 2.3% of patients in the Isa-Kd group and 0.8% in the Kd group.

In relapsed and refractory multiple myeloma clinical trials, herpes zoster was reported in 2% of patients. In ICARIA-MM, the incidence of herpes zoster was 4.6% in the Isa-Pd group compared to 0.7% in the Pd group, and, in IKEMA, incidence was 2.3% in the Isa-Kd group compared to 1.6% in the Kd group.

Cardiac failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary edema) was reported in 7% of patients with the Isa-Kd group (grade ≥3 in 4%) and in 7% of patients with the Kd group (grade ≥3 in 4.1%). Serious cardiac failure was observed in 4% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group. See the current prescribing information for carfilzomib for more information.

7 DRUG INTERACTIONS

7.1 Laboratory Test Interference

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA *[see Warnings and Precautions (5.4)]*. In patients with persistent very good partial response, where interference is suspected, consider using an FDA-cleared isatuximab-irfc-specific IFE assay to distinguish isatuximab from any remaining endogenous M protein in the patient's serum to facilitate determination of a complete response.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria *[see Warnings and Precautions (5.4)]*.

SARCLISA®
(isatuximab-irfc) injection, for intravenous use

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on SARCLISA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program.

Clinical Considerations

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Defer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

Data

Animal data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

8.2 Lactation

Risk Summary

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

SARCLISA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment and for 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness of SARCLISA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 56% (586 patients) were 65 and over, while 16% (163 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years and over and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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Campion breaks down those she's found helpful in her practice below.

Recommend hydration and good nutrition

While Campion says there's no specific diet recommended for MM patients, adopting a well-balanced, nutrient-dense meal plan can help anyone feel better, so it makes sense to counsel patients on such an approach. Think a good mix of unprocessed foods with lots of colorful vegetables and lean protein. "Water intake is also something to look at," says Campion. "As long as there aren't fluid restrictions from a cardiac standpoint, staying well hydrated may help." The American Cancer Society's nutrition guides can be a good place to point a patient for more guidance.

Encourage exercise

While MM patients may not always feel motivated to exercise, Campion insists she's seen benefits when patients "stay moving as much as possible." She adds, "From the fatigue standpoint, it can help patients avoid muscle wasting and encourage the body to stay at the right point in the circadian rhythm, so it may help patients sleep well." Plus, as a 2023 literature review in the *Journal of the Advanced Practitioner in Oncology* points out, study participants who are active often show better measures of fatigue, pain and mood.

Of course, every patient is different, and the amount and type of activity for each one should be tailored to them. However, generally, Campion recommends low-impact exercise. "Cycling tends to be something that our patients can do and enjoy. Swimming is one of the best things–a full body workout and no impact as far as joints. Walking is another–we encourage patients to take even just a 15- to 20-minute walk a day."

Helping patients focus on something to look forward to–and work toward–can keep them moving as well. "I ask if there's something specific you want to be doing that you can no longer do–like pickleball, golf or spending time with grandkids without exhaustion," she says. Identifying something to build strength and stamina toward can help keep them motivated–and meeting those goals can improve their quality of life.

Treat anemia

Between 60% and 70% of patients have anemia at the time of diagnosis, according to the International Myeloma Foundation, which contributes to the weak and tired feeling. How Campion tackles anemia depends on the cause. If it's present at diagnosis, treating the myeloma may correct it, but for those experiencing it as a side effect of medication or who have a concurrent issue with iron deficiency, she suggests replacing it with a supplement.

Suggest a massage

"Massages are great self-care," insists Campion. When it comes to aches and pains, a trip to a massage therapist may be helpful; however, a practitioner should take care in the kind they recommend to cancer patients. "Generally, a relaxation massage will be okay; however, we guide our patients to avoid deep tissue massage," says Campion. That type of treatment can be too rough for those with MM.

Talk about sleep

"A lot of times if your pain is uncontrolled, it affects sleep," says Dr. Campion. "Taking steroids as part of treatment can impact it. But you also just have stress around the diagnosis–thinking about the treatment, what's coming next what's coming down the road can keep people up." For help for the last point, Campion suggests reaching out for counseling or support groups either online or in their area to help manage feelings of isolation and provide an outlet to talk about stress, anxiety and depression.

Her other recommendation: going over good sleep hygiene with the patient. "This includes limiting screen time before bed and trying to have a set bedtime routine to get your brain and body ready to sleep," she says.

Greenlight taking it easy

It may seem obvious to suggest rest to patients, but it's easy to overlook–and having a care provider encourage it may be just the catalyst a patient needs to make it a priority. "I think that's so important. Your body is going through a lot, especially while on active treatment," Campion says. While encouraging exercise is important, she tells her patients: "If your body is tired and telling you to take a nap, it's time to pause!"

Emphasize stress relief

Stress is not a friend to anyone grappling with pain or fatigue. Keeping it in check can be very helpful, says Campion, "Especially early on in the first cycle or two of treatment," when there are many unknowns, and patients "are glued to the results of their treatment." Acupuncture, yoga and meditation are all on her list of recommendations. She also encourages patients to tell their doctors exactly what thoughts and questions may be keeping them up at night. She tells them: "Don't sit on it, stressing about the what-ifs! Send us a message through the charting system, and we'll respond."

Illustration by Alex Nabaum

Consider pain-relief interventions

Some patients who are experiencing pain and fatigue from MM may benefit from the addition of certain therapies to their care plan. For example, radiation therapy. Explains Campion, for people with large and painful lesions, "Radiation therapy decreases the activity at the lesion, and the myeloma is essentially dead at that spot." It can also be helpful in targeting masses because "it decreases the size [of the mass] so it's not pressing on the nerve."

Vertebroplasty (in which bone cement is injected into problem vertebrae) and kyphoplasty (a similar procedure using inflatable balloons) have also proven to be effective pain relief in treating fractures, and a 2023 study found their outcomes to be equally effective in their outcomes on pain relief and quality of life improvements.[5]

Keep a calendar

Campion's last suggestion for managing pain and fatigue: Helping a patient identify if their medication is a contributing factor. She does that by having her patients record how they're feeling on a calendar. "We like to use calendars because some patients use a calendar to keep track of medications already. It's nice to use that also for recording side effects and how it's related to the cycle at all–if the effects are drug-related I would expect symptoms to build at the beginning of the drug cycle." This can help her adjust doses or make decisions about what strategies to recommend from there.

–by Beth Shapouri

References

1. **Nielsen LK, et al. Health-related quality of life in patients with multiple myeloma participating in a multidisciplinary rehabilitation program. *Ann Hematol*. 2021;100(9):2311-2323.**
2. **Wilson Rogers LP, et al. Are pain and fatigue in multiple myeloma related to psychosocial factors?: a systematic review. *Cancer Nurs*. 2020;43(3):E121-E131.**
3. **Hillengass M, et al. J. Physical activity in multiple myeloma: a review of the current literature. *J Adv Pract Oncol*. 2023;14(2):153-158.**
4. **Tsang RW, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the international lymphoma radiation oncology group. *Int J Radiat Oncol Biol Phys*. 2018;101:794-808.**
5. **Garnier J, et al. Kyphoplasty versus vertebroplasty in osteoporotic thoracolumbar spine fractures. Short-term retrospective review of a multicentre cohort of 127 consecutive patients. *Orthop Traumatol Surg*. 2012;6:S112-S119.**

PATIENT: WAYNE, 69, WAS DIAGNOSED WITH MM IN 2012. HIS MEDICAL HISTORY WAS NOTABLE FOR CORONARY ARTERY DISEASE WITH A HISTORY OF 3 STENTS, HEART FAILURE WITH PRESERVED EJECTION FRACTION, ATRIAL FIBRILLATION, HYPERTENSION AND TYPE 2 DIABETES.

"We had to consider his high-risk features before starting second-line therapy"

PHYSICIAN:

Patrick Hagen, MD

Associate Professor of Medicine, Division of Hematology & Oncology, Loyola University Medical Center, Maywood, IL

History:
In 2012, Wayne presented to the hospital complaining of progressive lower back pain with radiation to the front of his abdomen for the previous two months. He was prescribed physical therapy and OTC pain medication without improvement. Eventually his symptoms worsened to the point that he needed a walker.

Wayne was sent for an MRI, which revealed a T10 compression fracture with associated soft tissue abnormality and renal lesion suspicious for malignancy. He was then transferred to our medical center to have surgery for his fracture. His pathology report revealed a plasmacytoma.

Wayne, married with one son, retired four years ago. He and his wife enjoyed gardening, and every few weeks they drove an hour to visit their son and two grandchildren. However, Wayne's recent symptoms, including increasing fatigue and exacerbation of chronic back pain, had prevented him from doing what he enjoyed.

When Wayne came to see me, his initial serum studies showed immunofixation electrophoresis with a monoclonal IgG-kappa M-protein with a suppressed albumin and normal B2-microglobulin. Bone marrow biopsy showed >30% plasma cell monoclonality and a negative MM FISH panel. A skeletal survey was unremarkable, other than the already known T10 lesion. Based on these results, Wayne's diagnosis was IgG-kappa MM R-ISS stage II. We discussed treatment, including potential adverse effects. He started on bortezomib and dexamethasone, completing seven cycles of therapy, which he tolerated well. Bone marrow biopsy after cycle 6 did not show significant reduction in tumor burden, so lenalidomide was added, which he tolerated well, other than fatigue. Subsequently he achieved a very good partial response (VGPR) to induction therapy. After receiving 11 cycles of chemotherapy and autologous stem cell transplantation (ASCT), he was put on maintenance therapy with lenalidomide. Adjunct treatments included denosumab.

Wayne remained in remission for nearly 10 years. Unfortunately, two years ago he relapsed following increasing fatigue, exacerbation of chronic back pain, and recurrent infections. Serum studies showed M-protein had reappeared and kappa and lambda free light chains had increased, among other signs of progression. Bone marrow biopsy showed 67% plasma cells and MM FISH panel was positive for del17p, a high-risk chromosomal abnormality.

NEW!
KOL ON DEMAND VIDEO
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Initiating treatment:
Wayne and I discussed second-line therapy, including adverse effects. He was a good candidate for a regimen that included isatuximab, as recent data have shown significantly prolonged progression-free survival in high-risk patients. We started Wayne on isatuximab-carfilzomib-dexamethasone (KRd), which he tolerated well.

After eight cycles, he showed VGPR and bone marrow showed no clonal plasma cells. He also had clinical improvement with increased energy, minimal back pain and no more infections. He had a repeat bone marrow biopsy showing he was in complete response with no detectable malignant plasma cells in the bone marrow, but MRD testing was positive, indicating minimal residual disease activity. He received a second ASCT and was put on maintenance therapy with isatuximab. At his one-month follow-up, Wayne said he felt better and was back to his normal activities, for which he and his wife were grateful. He is now 18 months post-transplant and remains on isatuximab maintenance and in complete response.

Considerations:
While there has been significant advancement in treatments for MM, unmet needs remain. High-risk patients continue to have suboptimal outcomes, including patients who are older, have high-risk chromosomal changes, have impaired kidney function, and those who are refractory to multiple drug classes.

In a subgroup analysis of the IKEMA trial, treatment with isatuximab + KD after early relapse of MM resulted in median progression-free survival for approximately 42 months in a patient population enriched with high-risk genomics including del17p. After relapse, it's critical to use the most efficacious treatment early rather than reserving it for third-line or later therapy in order to achieve the deepest and longest remissions. For high-risk patients like Wayne, prioritizing a regimen with the highest long-term efficacy can improve outcomes and help them live as well as possible. In addition, the combination of isatuximab + KD is well tolerated and rarely leads to adverse events requiring dose reductions or discontinuation of therapy, which for a patient like Wayne (and most MM patients over the age of 70) is critical due to his many comorbidities. ●

"At his one-month follow-up, Wayne said he felt better and was back to his normal activities, for which he and his wife were grateful."

Illustration by Juhee Kim

Q&A

Insight on managing multiple myeloma

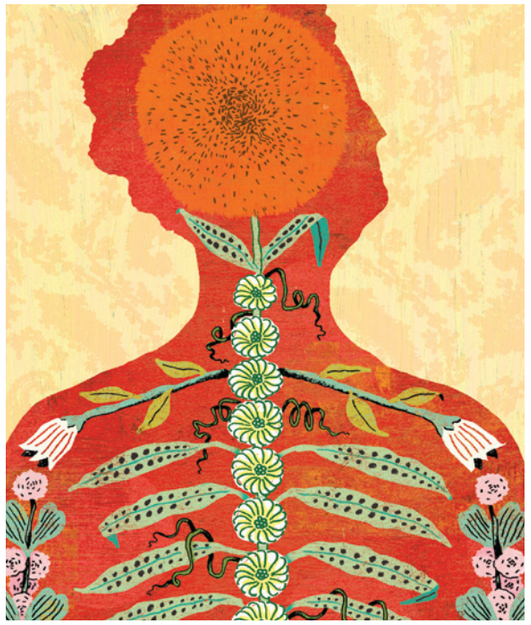

Illustration by Ken Orvidas

Helping patients cope

Q: Are there aspects of living with MM that HCPs may not fully appreciate or address?

A: Living with multiple myeloma (MM), a complex and often unpredictable cancer, introduces a variety of challenges that may extend beyond the immediate scope of medical treatment. Healthcare professionals (HCPs) might sometimes overlook the full impact of the disease, particularly the psychological, social and long-term management aspects that significantly influence patient well-being. Patients with multiple myeloma often endure chronic pain and fatigue, which can severely limit daily functioning and diminish quality of life. Moreover, the emotional and psychological toll of managing a chronic, life-threatening illness can lead to significant stress and mental health issues, potentially affecting patient adherence to treatment protocols and overall treatment outcomes.

To address these multifaceted challenges, it is crucial for HCPs to adopt a holistic care approach. This approach should include regular and thorough assessments of physical symptoms like pain and fatigue, as well as the provision of comprehensive support services. Referrals to pain management specialists and palliative care should be made when necessary to help manage symptoms effectively. Furthermore, emotional and psychological support through counseling services and support groups should be readily available to help patients cope with the mental health challenges posed by the disease.

Educational initiatives are also essential. By thoroughly informing patients about the nature of multiple myeloma and involving them in treatment decisions, HCPs can empower patients, enhancing their engagement and compliance with treatment plans. Employing a multidisciplinary team approach—integrating the expertise of oncologists, nurses, social workers, and psychologists—is vital. Such teams can work collaboratively to address the comprehensive needs of multiple myeloma patients, ensuring that all aspects of the disease are managed, from the physical to the psychosocial. This integrative strategy not only improves the care experience, but also optimizes clinical outcomes, paving the way for a more patient-centered approach to chronic cancer management.

–Francisco J. Esteva, MD, PhD, *Chief, Division of Hematology and Medical Oncology at Lenox Hill Hospital, New York City*

MRD assessment

Q: What is the role of MRD in the treatment of MM?

A: Minimal residual disease (MRD) status is increasingly being used to assess treatment response, with MRD negativity correlating with better patient outcomes. MRD assessment tools in MM represent the wave of the future, with prognostic roles over the entire course of the disease. MRD performance holds throughout different clinical contexts and treatment scenarios, being predictive irrespective of the disease setting—newly diagnosed for transplant eligible and ineligible patients or relapsed/refractory—at various sensitivity thresholds and cytogenetic risks. Ultimately, using MRD tools as early surrogate markers of long-term outcomes such as overall survival will help us define the optimal management of all MM patients at all stages of the disease process. Rather than single-time-point assessments, sustained MRD negativity over a longer period of time is likely the more important goal in disease management.

–Muhamed Baljevic, MD, *Director of Plasma Cell Disorders Research and Vanderbilt Amyloidosis Multidisciplinary Programs, Vanderbilt University Medical Center, Nashville*

Early detection

Q: What is smoldering multiple myeloma, and how do you monitor these patients?

A: Smoldering multiple myeloma represents a critical, precancerous stage in the development of multiple myeloma, positioned between monoclonal gammopathy of undetermined significance (MGUS) and symptomatic multiple myeloma. Unlike MGUS, which has a lower risk of progression, smoldering multiple myeloma is characterized by a greater burden of malignant plasma cells, but does not manifest organ damage or overt symptoms typically associated with active multiple myeloma. Therefore, while immediate treatment may not be necessary, vigilant patient monitoring is essential due to the elevated risk of progression to active disease, which stands at approximately 10% per year for the first five years following diagnosis.

Monitoring patients with smoldering multiple myeloma is a complex, multifaceted process aimed at early detection of disease progression to initiate timely treatment and mitigate potential complications. This surveillance includes regular clinical assessments and diagnostic evaluations. Blood tests are routinely conducted to measure levels of monoclonal proteins, which are indicative of the plasma cell population dynamics. Additionally, bone marrow biopsies are performed periodically to assess cellular changes and progression risk more directly.

Imaging studies, such as MRI or CT scans, play a crucial role in detecting early signs of bone damage or other structural abnormalities that could suggest a transition toward symptomatic myeloma. The frequency and intensity of monitoring are tailored based on individual risk assessments, which incorporate specific biomarkers and disease characteristics. Patients deemed at high risk of progression might undergo more frequent testing and closer clinical observation. This proactive monitoring strategy is vital in managing patients with smoldering multiple myeloma, as it allows healthcare professionals to swiftly address any changes in the disease state, thereby optimizing patient outcomes and preparing for potential treatment initiation at the earliest signs of active myeloma.

–Francisco J. Esteva, MD, PhD

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Muhamed Baljevic, MD, Associate Professor of Medicine, Director of Plasma Cell Disorders Research and Vanderbilt Amyloidosis Multidisciplinary Programs (VAMP) at Vanderbilt University Medical Center in Nashville

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Clinician Update

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DECISION TOOL

Treating early relapse of MM: considerations for therapy

There are no clear-cut guidelines for treating early relapse of multiple myeloma (MM), typically defined as relapse after one to three prior lines of therapy. Fortunately, a variety of treatment options is available, including novel regimens that have been proven to prolong progression-free survival in high-risk patients. However, along with these options comes the challenge of weighing a regimen's efficacy with the biology of the disease, nature of the relapse and treatment history, among other factors. To help physicians and patients decide on next steps for treating early relapse, the International Myeloma Foundation recommends taking the following into account:

GUIDING PRINCIPLES:

1. Incorporate patient preference based on shared decision-making.
2. Use three-drug combinations as long as possible, substituting at least one new agent—two if high-risk early relapse.
3. Employ the regimen with the greatest probability for longest duration of remission while taking all other factors into consideration.

KEY CONSIDERATIONS WHEN TREATING AN INDIVIDUAL PATIENT:

Patient-specific characteristics such as:

- Age
- Frailty
- Presence of certain comorbidities, such as renal impairment

Disease-related factors such as:

- How fast the myeloma is progressing
- Presence of high-risk genetic markers
- Location, such as extramedullary disease

Treatment-related factors such as:

- Response to prior therapies
- Side effects of prior therapies
- Development of disease refractory to early treatment regimens
- Practical considerations, such as access, cost and scheduling

NOTE: Not a complete list. For more details, visit the International Myeloma Foundation (*myeloma.org*) and consult the latest guidelines from the National Comprehensive Cancer Network (*nccn.org*).