A Focus on Relapsed Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a relapsing disease for many patients with multiple myeloma. At relapse, patients have many options for treatment once disease has progressed. Advanced practitioners are well suited to set expectations for ongoing therapy and underscore the importance of continued disease monitoring. Criteria for relapsed myeloma rely on biomarker and radiologic imaging, as well as physical exam and awareness of new bone pain or changes in physiologic function. The treatment of patients with relapsed MM requires a personalized approach and considers patient desires in regard to aggressiveness of therapy and willingness to participate in a clinical trial. The prognosis of patients with relapsed MM depends upon disease characteristics at baseline or throughout, as patients may acquire adverse cytogenetic abnormalities through various lines of treatment. Empowering patients to understand their diagnosis, interpret labs, and take an active role in treatment selection through shared decision-making can improve patients' quality of life and enhance adherence.

CASE STUDY

Wesley is a 68-year-old male who had just retired as a French teacher when he was diagnosed with IgG kappa multiple myeloma, standard risk by cytogenetics, in 2014. He was initially treated with lenalidomide, bortezomib, and dexamethasone (RVd) and achieved a very good partial remission. He then underwent an autologous stem cell transplant. At 3 months following transplant, he was treated with maintenance lenalidomide at 10 mg po days 1 to 28 (NCCN, 2021). He achieved a complete remission after 8 months of therapy. In the beginning, Wesley tolerated lenalidomide maintenance well. He had no appreciable cytopenias. The nurse navigator worked with Wesley to secure copay assistance through a patient assistance foundation.

Unfortunately, after 24 months of lenalidomide maintenance, Wesley developed diarrhea. He learned to take cholestyramine powder once every morning for prevention of lenalidomide-induced diarrhea. With the help of a food diary, he learned to minimize certain fruits and vegetables in his diet that had been exacerbating the diarrhea (Faiman et al., 2017). Occasionally, he needed to take loperamide up to 8 mg per day to abort the diarrhea when he had more than three stools per day over his baseline. After 5

years of maintenance, he wanted to take a break from treatment. He discussed his concerns with his main oncology team, which included an oncologist, advanced practitioner (AP), and nurse. Based on the deep remission and nearly 5 years on lenalidomide maintenance, he decided to take a planned treatment holiday. The diarrhea improved after 5 months, and as he continued to

have no evidence of paraproteins in his serum or urine, he opted to stay off lenalidomide.

Diagnosis of Relapsed MM

Wesley had been walking 2 to 3 miles a day and remained active. It was his lifelong goal to spend 1 month traveling through France with his wife. He was skeptical about his ability to travel after

Table 1. Results of Lab Testing and Criteria for Relapse

Clinical relapse requires ≥ 1 of the following criteria:
- Increase in the size of existing plasmacytomas or bone lesions
- Hypercalcemia (> 11 mg/dL)
- Hgb ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions
- SCr ≥ 2 mg/dL from the start of the therapy and attributable to myeloma
- Hyperviscosity related to serum protein
- Increase of 25% from the lowest confirmed response value in n ≥ 1 of the following criteria:
  - » Serum M-protein ≥ 0.5 g/dL
  - » Urine M-protein ≥ 200 mg/24 hours
  - » If no serum or urine M-protein can be measured, the difference between monoclonal and polyclonal FLC levels must increase by > 10 mg/dL

Follow-up and surveillance tests
- CBC with differential
- Electrolytes; metabolic panel
- SCr and corrected serum Ca^{2+}
- M-proteins and immunoglobulins
- Serum FLC as clinically indicated
- Bone marrow aspiration and biopsy
- Assess MRD

Imaging as clinically indicated
- Consider using the same imaging modality during initial workup
- Whole body low-dose CT
- Whole body MRI
- Whole body FDG PET/CT

Note. Hgb = hemoglobin; SCr = serum creatinine; FLC = free light chain; Ca2+ = calcium; MRD = minimal residual disease; FDG = fluorodeoxyglucose. Information from Kumar et al. (2016); NCCN (2022).

Table 2. Suggested Treatment Options in Patients With MM: One to Three Relapses

Class	Agent	Mechanism of action
Immunomodulatory agents (IMiDs)	Thalidomide Lenalidomide Pomalidomide	• Both direct and indirect immunomodulatory effects through activation of T cells and NK cells • Blocks adhesion molecules between the myeloma cells and the bone marrow stroma
Proteasome inhibitors (PIs)	Bortezomib Carfilzomib Ixazomib	• Inhibition of the proteasome results in the cell's inability to undergo protein degradation leading to apoptosis
Monoclonal antibodies (mABs)	Daratumumab (human anti-CD38) Isatuximab (chimeric anti-CD38 Elotuzumab (humanized anti-SLAMF7)	• Daratumumab and isatuximab bind to CD38 leading to apoptosis via antibody-dependent cellular toxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis • Elotuzumab binds to SLAMF7 on the surface of the myeloma cells and NK cells. Upon binding to the myeloma cell, it targets it for recognition by the NK cells leading to apoptosis
Selective inhibitors of nuclear export (SINE)	Selinexor	• Binds to and inhibits nuclear export protein, which leads to cell cycle arrest and apoptosis of cancer cells
BH3 mimetics	Venetoclax only for t(11;14)	• BCL-2 inhibitor that induces cell death in multiple myeloma (MM) cells, particularly in those harboring t(11;14), which express high levels of BCL-2 relative to BCL-XL and MCL-1
Chemotherapy	Cyclophosphamide Melphalan	• Alkylating chemotherapy agent used in combination with other myeloma therapies

Note. Information from Nijhof et al. (2017); NCCN (2022); Kumar et al. (2017); Jackson et al. (2019); Palumbo et al. (2010); Moreno et al. (2019); Laubach et al. (2015).

his diagnosis, but over the past 5 years, his disease was stable, and he was finally off all therapy. Therefore, he made plans to travel to Europe. Recently, he noted an increase in thoracic spinal pain when walking only 15 minutes. He reported this pain to his oncology team and further testing was ordered. The results of his lab work revealed normal complete blood count, comprehensive metabolic panel, and beta-2 microglobulin. No new skeletal lesions were noted on PET scan. His monoclonal (M) spike was not detected since autologous stem cell transplant, but his most recent M spike trend over 4 months was 0.2 g/dL to 0.4 g/dL and now 0.8 g/dL. Table 1 shows International Myeloma Working Group criteria for relapse and recommended testing. No other lab or radiologic abnormalities were present, which qualifies for biochemical disease progression.

Based on these results, his oncology team determined that Wesley should resume antimyeloma, plasma cell–directed treatment. He had been off lenalidomide for 2 years at this point, and therefore was not considered refractory to lenalidomide. Wesley asked if he could just resume lenalidomide as his diarrhea resolved, as it was "working" when he stopped the drug, but his oncology team suggested that a combination therapy including different drugs was likely to be more effective than just resuming lenalidomide at this relapse. The AP sat with Wesley and his wife, and reviewed numerous treatment options at first relapse (Table 2).

Although multiple myeloma (MM) remains an incurable disease, the development of novel therapies since the early 2000s has improved the overall survival for myeloma patients. Over the past 10 years, survival rates of MM have significantly improved and are in the range of approximately 6 years. It is estimated that more than 80% of patients who are eligible for autologous transplant live longer than 4 years (Attal et al., 2017; Durie et al., 2017).

Almost all patients treated for MM will relapse, and the duration of response decreases with each relapse. Harousseau and Attal (2017) report that since triple therapy combinations, including one immunomodulatory drug (IMiD), one proteasome inhibitor (PI), and dexamethasone, have been used in combination with maintenance therapy, the depth of response and increased numbers of complete responses have greatly improved overall survival and progression-free survival rates.

In this case study, Wesley relapsed 7 years after his initial treatment and was not on maintenance therapy at the time of slow, biochemical relapse. Therefore, Wesley has numerous treatment options and several factors which should be considered. The acronym TRAP (Timing of the relapse, Response to prior therapy, Aggressiveness of the relapse, and Performance status) is helpful in determining treatment strategies (Rajkumar, 2018). Currently, combination drug therapy with three to four therapies is preferred for relapsed MM (Moreau et al., 2021). Figure 1 depicts a decision algorithm based on consensus recommendations from the International Myeloma Working Group (IMWG).

Goals of therapy should be evaluated for all patients with multiple myeloma. There are numerous factors to consider at the time of relapse. High-risk features of relapse should be considered, such as high-risk cytogenetic findings, aggressiveness of CRAB criteria (Calcium elevation, Renal dysfunction, Anemia, and Bone disease), comorbidity, and the patient's preferences (Nijhof et al., 2017). Ultimately, a shared decision model is the optimal approach when considering future treatment options. Shared decision-making occurs when both the patient and the health-care provider collaborate to develop a treatment plan that works best for the patient. The discussion includes data-driven treatment, the provider's experience in treatment of the disease, as well as the values and preferences that are important to the patient (Faiman & Tariman, 2019; Steffensen et al., 2018).

Not all people living with MM value the same treatment attributes equally. Fifer and colleagues (2020) conducted an online survey of 124 people with MM in Australia. The survey also included 44 caregivers, 28 hematologists, and 34 nurses involved in the care of patients with MM. The survey used discrete choice ex-
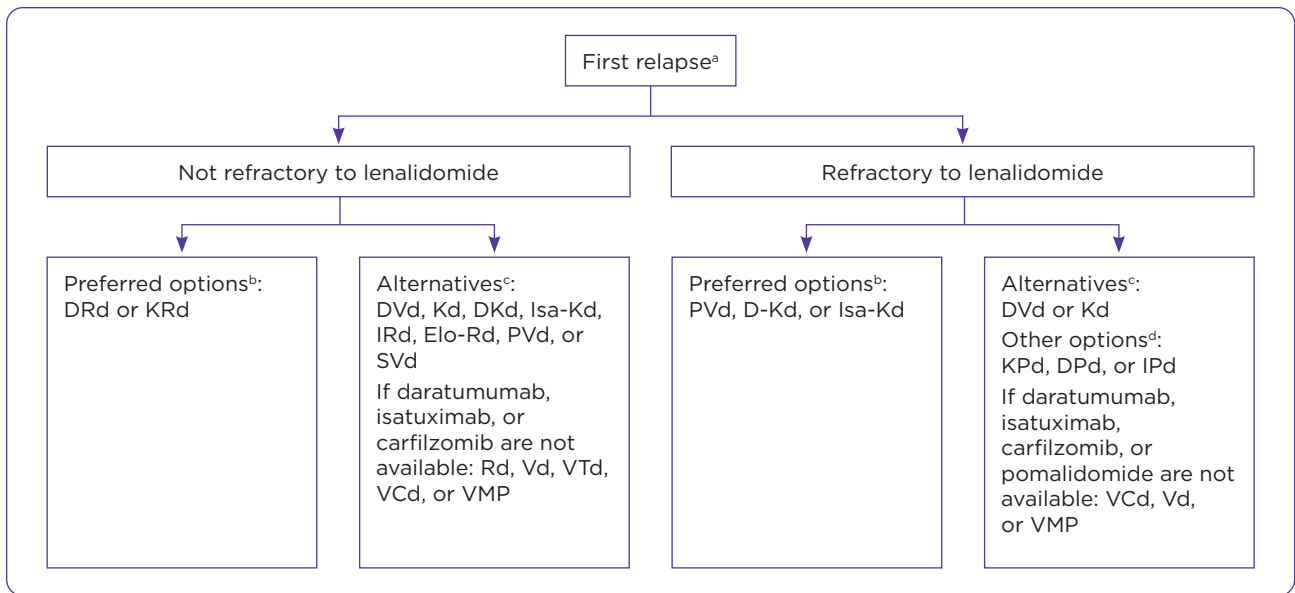
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                          ┌─────────────────────┐
                          │   First relapseᵃ    │
                          └─────────────────────┘
            ┌─────────────────────────┴─────────────────────────┐
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  │  Not refractory to lenalidomide│         │   Refractory to lenalidomide   │
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Preferred optionsᵇ: DRd or KRd	Alternativesᶜ: DVd, Kd, DKd, Isa-Kd, IRd, Elo-Rd, PVd, or SVd If daratumumab, isatuximab, or carfilzomib are not available: Rd, Vd, VTd, VCd, or VMP	Preferred optionsᵇ: PVd, D-Kd, or Isa-Kd	Alternativesᶜ: DVd or Kd Other optionsᵈ: KPd, DPd, or IPd If daratumumab, isatuximab, carfilzomib, or pomalidomide are not available: VCd, Vd, or VMP

Figure 1. Decision algorithm for first relapse of myeloma based on International Myeloma Working Group guidelines. Adapted from Moreau et al. (2021). DKd = daratumumab, carfilzomib, dexamethasone; DPd = daratumumab, pomalidomide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Elo-Rd = elotuxumab, lenalidomide, dexamethasone; IPd = ixazomib, pomalidomide, dexamethasone; IRd = ixazomib, lenalidomide, dexamethasone; Isa-Kd = isatuximab, carfilzomib, dexamethasone; Kd = carfilzomib, dexamethasone; KPd = carfilzomib, pomalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone; Rd = lenalidomide, dexamethasone; SVd = selinexor, bortezomib, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; Vd = bortexomib, dexamethasone; VMP = bortezomib, melphalan, prednisone; VTd = bortezomib, thalidomide, dexamethasone.
ᵃConsider salvage auto-transplantation in eligible patients.
ᵇGrade of recommendation: 1A.
ᶜGrade of recommendation: 1B.
ᵈGrade of recommendation: 1C.

periments to quantify preferences for treatment. Overall survival, remission period, and annual out-of-pocket cost had the most variation. Caregivers were less cost sensitive than the MM patients and were more concerned with quality of life. Physicians and nurses were more concerned with survival and were more cost-conscious than the patients.

The Agency for Healthcare Research and Quality (AHRQ) recommend a "SHARE" approach to ensure clinicians are employing the concept of shared decision-making in the care of patients. Briefly, the five steps are (AHRQ, 2014):

- Seek your patient's participation
- Help your patient explore and compare treatment options
- Asses your patient's values and preferences
- Reach a decision with your patient
- Evaluate your patient's decision.

HEALTHY BEHAVIOR AND PROMOTION OF WELLNESS

Advanced practitioners are in a pivotal position to encourage patients towards adopting healthy lifestyles to maximize wellness. Incorporating this discussion when caring for the myeloma patient is key. Glenn (2020) provides a strategy for motivational interviewing to include open-ended questions, reflective listening, and affirming, supportive, and summarizing statements to engage patients in behavior change. Glenn also suggests using the 5As template to guide clinical interventions (Table 3; Goldstein et al., 2004).

Applying the 5As model to promote healthy behavior and wellness guides the advanced practitioner to ask about addictive behaviors such as alcohol, drugs and tobacco, dietary habits, physical activity, and sun exposure. The importance of assessing physical activity is validated in a re-

cent study conducted by Gilchrist and colleagues (2020). In this prospective study, higher levels of sedentary time were associated with a significant increase of cancer mortality compared with people who had an active lifestyle.

PATIENT SATISFACTION AND QUALITY OF LIFE

Chari and colleagues (2019) conducted a pilot observational study to determine factors associated with patient-reported satisfaction in patients with relapsed/refractory multiple myeloma (RRMM). An Eastern Cooperative Oncology Group (ECOG) performance status of > 2 (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours) was associated with lower global satisfaction and perceived effectiveness of treatment (NCI, 2020). Performance status was a main predictor of patient-perceived global satisfaction, as well as patient-perceived treatment effectiveness. Additionally, an all-oral treatment regimen not only predicted shorter time burden but also how patients perceived treatment convenience.

PSYCHOLOGICAL IMPACT OF DIAGNOSIS AND RELAPSE

Individuals diagnosed with MM will endure disease- and treatment-related complications throughout the trajectory of their disease. It is common for patients to receive continued treatment with little time away from treatment. Patients may respond to therapy for a period of time, and then be confronted with disease progression or relapse. Unfortunately, the patient is forced to continually adapt to the many challenges posed by this illness and its treatment regimens (Cormican & Dowling, 2018). Faced with long-term side effects for patients, the evolving challenge in myeloma management is weighing disease progression with quality of life (Kiely et al., 2017).

It is estimated that approximately 25% of patients with MM are diagnosed with psychological distress and symptoms associated with depression. The psychosocial dimensions of health-related quality of life (HRQOL) are a prognostic indicator for patients experiencing psychological issues. For this reason, it is important to assess the psychosocial status of the MM patient (Maatouk et al., 2018). There is a paucity in research to describe the emotional experiences of the MM patient at the time of first and subsequent relapse in disease.

A qualitative study by Hulin and colleagues (2017) found that MM patients at first relapse described it as the most profound period of time in terms of negative emotions. Hopelessness, devastation, and resignation were often associated with the time of first relapse. Other common descriptors used during this period were scared, depressed, worried, confused, sad, and frustrated. The negative emotions of disease progression in the first relapse for MM patients were described as more devastating than the initial MM diagnosis. It is interesting that the majority of patients in the Hulin study (2017) reported that the emotions associated with subsequent relapses improved compared with the emotions during the first relapse, since patients learned what to expect.

Table 3. 5 As Model to Promote Healthy Behaviors

- **Assess** the patient's physical activity during the past 7 days.
- **Advise** the patient to engage in moderate-intensity physical activity for 150 to 300 minutes or vigorous-intensity physical activity for 75 to 150 minutes, if possible. This advice should be simple. The patient's personal and medical situation needs to be taken into account, such as potential risk for injury, bleeding, etc.
- **Agree** on whether the patient is ready for the recommended physical activity; if the patient is not ready, then this is not the time to pursue this further. If the patient is, then proceed to the next step.
- **Assist** the patient in developing specific and feasible goals for physical activity with the recommendation of a physician or physical therapist. Ask about logistical, financial, and psychosocial barriers to the activity, and explore strategies to mitigate them.
- **Arrange** for the patient to receive physical therapy, occupational therapy, or other support as needed. Discuss a plan to follow up with the patient to support their progression.

Note. Information from Gilchrist et al. (2020).

CASE STUDY TREATMENT AND OUTCOME

As mentioned in the case study, Wesley and his wife wanted to spend 1 month traveling throughout France. They finally booked the trip 3 months out. Several options were considered, including combinations containing monoclonal antibodies such as isatuximab, daratumumab, and elotuzumab. In collaboration with his health-care team, Wesley opted for ixazomib 4 mg po days 1, 8, and 15 every 28 days; lenalidomide 25 mg po days 1 to 21 every 28 days; and dexamethasone 20 mg po weekly due to his slow, biochemical relapse and desire for an all-oral regimen to allow for travel. He decided that if this three-drug regimen did not control his MM, then he would postpone their trip and participate in a clinical trial with a monoclonal antibody, proteasome inhibitor, and corticosteroid.

After 2 months, Wesley's M-protein had decreased by 90%, achieving a very good partial response. He was feeling more hopeful about his future and was now able to travel and fulfill his lifelong dream of traveling around France for an extended period.

CONCLUSION

Although advancements in MM treatments have resulted in improved survival rates, MM remains incurable. There is an unmet need to address the emotional needs of myeloma patients and improve the overall patient experience during the relapsed phase of disease. It is not uncommon for the relapsed MM patient to feel hopelessness and devastation. In this case, Wesley was able to work with his clinical team and discuss what was important to him. Once he responded to therapy, his physical, psychological, and emotional status improved, and he was well enough to fulfill his goal of traveling to France. ●

Disclosure

Dr. Faiman has served as a consultant for Bristol-Myers Squibb, GSK, Janssen, Karyopharm, Legend Biotech, Oncopeptides, Sanofi, and Takeda. Dr. Noonan and Ms. Rome have no conflicts of interest to disclose.

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