A Focus on Newly Diagnosed Multiple Myeloma

KEVIN BRIGLE,[1] PhD, ANP, DANIEL VERINA,[2] DNP, RN, ACNP-BC, and BETH FAIMAN,[3] PhD, MSN, APRN-BC, AOCN®, BMTCN, FAAN

From [1]VCU Massey Cancer Center, Richmond, Virginia; [2]Mount Sinai Medical Center, New York, New York; [3]Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Beth Faiman, PhD, MSN, APRN-BC, AOCN®, BMTCN, FAAN, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: faimanb@ccf.org

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Abstract

Multiple myeloma (MM) is an incurable plasma cell disorder that affects nearly 35,000 people annually. Over 149,000 individuals are estimated to live in the United States with MM. Research has generated a greater understanding of the pathology of this disease, now combined with mature clinical trial data that support the use of combination therapy in treatment. This article focuses on updated diagnosis, prognosis, and treatment of newly diagnosed patients. While the diagnosis of MM remains based on the 2014 International Myeloma Working Group (IMWG) guidelines, we review these and updated recommendations for the diagnosis and treatment of myeloma as well as relevant supportive care. The prognosis of patients with newly diagnosed MM relies heavily on the cytogenetic profile of the disease, along with other patient-specific risk factors. There are multiple first-line treatment options that combine three or four novel agents with the goal of reducing plasma cell burden and achieving minimal residual disease (MRD) negative status early in the treatment trajectory. Supportive care interventions aimed at minimizing the risk of infection and thromboembolic events, and protecting bone health are critical for maintaining quality of life and are as important as therapeutic treatment interventions.

CASE STUDIES

Case Study 1

Ms. B is a 53-year-old female with a medical history significant only for a remote appendectomy and vitamin D deficiency. She takes no medication except for a multivitamin and prescription vitamin D 50,000 IU weekly. She began to notice intermittent low back pain that progressed in intensity throughout the day, along with worsening fatigue and shortness of breath while climbing stairs. She presented to her primary care provider with these symptoms where she also described a more recent history of constipation, nausea, and mild confusion. Due to this constellation of symptoms, the primary care provider sent her to the local emergency department for evaluation and management. Table 1 shows results of her labs and imaging studies obtained in the emergency department.

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Table 1. Case Study 1: Relevant Lab and Imaging Results Obtained at the Local ED

Complete blood count
- WBC 1.4 K/µL
- Hgb 4.6 g/dL
- Platelets 92 K/µL (all low)

Chemistry panel
- Creatinine 3.4 mg/dL (elevated)
- Serum calcium 14.7 mg/dL (elevated)
- Albumin 3.2 g/dL (low)

Imaging
- Bone radiographs note multiple bilateral lytic lesions in the humeri and femurs.
- CT chest/abdomen/pelvis note multiple areas of bone destruction and cortical erosion involving multiple pedicles of the lumbar spine, iliac and ischial bones, the left 10th rib and left sacrum. Also noted is a 28 × 26 × 24 mm well-defined ovoid soft tissue mass surrounding the anterior left third rib and a questionable soft tissue mass at T3-T7.

Case Study 2

Whereas in the first scenario the patient presented with overt symptoms, it is not uncommon for asymptomatic patients to be diagnosed with multiple myeloma incidentally on physical exam, as in this second case. Mr. L is a 74-year-old retired landscaper with a past medical history of congestive heart failure, hypertension, hyperlipidemia, osteoarthritis, and obesity who presented to his primary care provider for his annual physical examination. He endorsed mild fatigue and noted "I feel fine, but I have been a little short of breath lately." He denied chest pain, edema, new bone pain, dysuria, or recent infections. At that visit, labs ordered by his primary care provider were significant for profound anemia (hemoglobin 6.3 g/dL) and an elevated serum total protein of 10.6 g/dL.

The incidence of multiple myeloma (MM) has increased over the past two decades. At the same time, the number of treatment options and their efficacy have increased significantly as well (Gulla & Anderson, 2020). While a growing number of patients are diagnosed with asymptomatic disease, the classic signs and symptoms of MM, including bone fractures, pain, hypercalcemia, acute renal failure, and anemia, remain common findings. Delays in diagnosis and the initiation of treatment place patients at risk of an exacerbation of symptoms and have the potential to result in irreversible organ damage and morbidity. Here, we present two common patient scenarios and discuss updates to diagnosis, staging, and treatment options (both therapeutic and supportive) for these patients.

CASE STUDY 1

Acute Management and Diagnosis

Ms. B was admitted to the hospital for treatment of hypercalcemia and further workup. She began hydration with normal saline 0.9% IV and was given subcutaneous (SQ) denosumab 120 mg × 1 dose for hypercalcemia of malignancy (Hu et al., 2014). As MM was the suspected diagnosis, she was started on dexamethasone 40 mg po × 4 days, and a comprehensive workup for multiple myeloma was performed (Table 2). Criteria for the diagnosis of active MM requiring initiation of therapy have been established by the International Myeloma Working Group (IMWG) and can be referenced by the SliM (≥ 60% clonal plasma cells [S], light chain ratio ≥ 100 [Li], MRI with more than one focal lesion [M]) CRAB (Calcium elevation, Renal dysfunction, Anemia, Bone lesions) mnemonic. The SliM criteria represent myeloma-defining events that were added by the IMWG that augment the classic CRAB criteria previously utilized to define active MM. Figure 1 shows updated diagnosis and staging information.

Treatment

During the acute, symptomatic phase of the disease, prompt initiation of systemic treatment and initiation of supportive care is essential. Ms. B began treatment with VCd: bortezomib 1.3 mg/m^2 SQ days 1, 4, 8, and 11 of a 21-day cycle; cyclophosphamide 300 mg/m^2 days 1, 8, and 15; and dexamethasone 40 mg po once weekly (NCCN, 2022). After completing her first cycle, Ms. B's serum creatinine improved to 1.4 mg/dL and estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2, and she was feeling much better. She and her family met with the outpatient oncology advanced practitioner (AP) to discuss treatment options.

The AP described several recent studies that evaluated treatment combinations for patients with newly diagnosed myeloma. At diagnosis, patients are generally defined as transplant eligible or transplant ineligible. It is important to note that transplant eligibility criteria are not absolute and can include patient preference in addition to performance status, comorbidities, and other factors. The article by Noonan, Rome, and Faiman (2022) in this supplement contains further discussion regarding treatment decision-making. Regardless of transplant eligibility, patients are further divided into categories according to low- or high-risk status of cytogenetic abnormalities (CA) present in their myeloma cells (NCCN, 2022). In general, patients will receive a three- or four-drug induction regimen based on fitness, frailty, CA, or even patient preference. An approach to selecting treatment options for patients with newly diagnosed transplant-eligible or transplant-ineligible patients is shown in Table 3.

The VCd regimen that was initiated for Ms. B is an effective and useful regimen for newly diagnosed patients with renal dysfunction. However, based on her CA in addition to her high disease burden, a more aggressive approach was considered. The AP reviewed data from studies utilizing the three-drug combination of carfilzomib, lenalidomide, and dexamethasone (KRd) and four-drug combination of daratumumab, lenalidomide, bortezomib, and dexamethasone (D-VRd; Gay et al., 2021; Voorhees et al., 2020; Laubach et al, 2021; NCCN, 2022). While the individual goals of treatment will vary with each patient, universal goals of all treatment regimens include the rapid control of the disease to minimize ongoing organ damage and achieve the deepest possible remission. After discussion with the AP and the oncology team, Ms. B opted for treatment with carfilzomib, lenalidomide, and dexamethasone (Gay et al, 2021). Clinical pearls for this regimen are outlined in Table 4. Following completion of cycle four, Ms. B's kappa

Table 2. Case Study 1: Relevant Lab, Pathology, and Imaging Results

- Serum light chains report kappa light chains 568 mg/L (elevated), lambda light chains 0.4 mg/L (low), and kappa:lambda ratio 142 (elevated)
- Beta-2 microglobulin 10.2 mg/L (elevated)
- LDH 214 units/L (normal)
- Bone marrow biopsy reports almost 100% cellularity with sheets of kappa restricted plasma cells > 90%.
- FISH positive for gain of chromosome 1q (+1q) and deletion of chromosome 17p [del(17p)]
- Diagnosis: Kappa free light chain multiple myeloma. R-ISS Stage III.

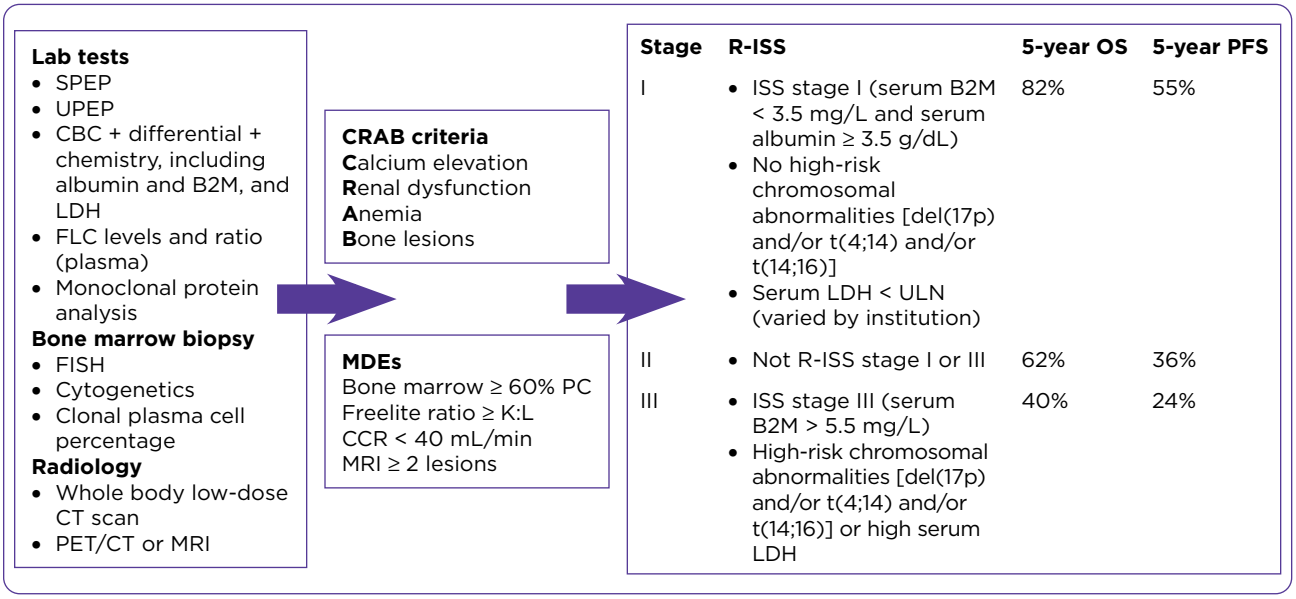

Figure 1. Labs, diagnosis, and R-ISS for MM. R-ISS = Revised International Staging System; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; B2M = beta-2 microglobulin; LDH = lactate dehydrogenase; FLC = free light chain; K:L = kappa:labda; FISH = fluorescence in situ hybridization; MDE = myeloma-defining event. CCR = creatinine clearance. Information from Palumbo et al. (2015).

Table 3. Considerations for the Treatment of Multiple Myeloma

Patient	Disease	Treatment	Regimen
• Age/frailty • Performance status • Lifestyle • Patient preference • Caregiver support • Comorbidities » Renal status » Neuropathy » Cardiac » Diabetes » Cytopenias	• Disease burden: ISS • Rate of progression • Marrow burden • CRAB symptoms • Extramedullary disease • Biology • LDH • Cytogenetics: » t(4;14) » del(17p) » t(14;16) » gain 1q or amp(1q) » t(11;14)	• Toxicity » Myelosuppression » Infections » Neuropathy » Secondary cancers » Ocular toxicity • Cost • Administration route • Relapsed vs. refractory • Depth/duration of response to prior treatment	• Triplet (eg., KRd) is preferred over doublet in high-risk patients • Include ≥ 1 agent from a new or nonrefractory class if relapsed disease • Previously used agents may be effective in different combinations • Treat to maximum response • Maintain on ≥ 1 agent until progression or intolerability

Note. CRAB = Calcium elevation, Renal dysfunction, Anemia, and Bone lesions; LDH = lactate dehydrogenase; KRd = carfilzomib, lenalidomide, and dexamethasone. Information from Laubach et al. (2016); NCCN (2022).

free light chains normalized and her cytopenias resolved. She then opted to proceed with autologous stem cell transplant (ASCT). She underwent an uneventful ASCT course and upon recovery was given the option of maintenance therapy with lenalidomide 15 mg po daily as standard of care or participating in an intergroup clinical trial randomizing patients to this standard of care with or without SQ daratumumab. She opted for the clinical trial and was randomized to maintenance with the lenalidomide and daratumumab combination.

Table 4. Clinical Pearls and Patient Education for Carfilzomib, Lenalidomide, and Dexamethasone (KRd)

- Planned dose escalation for most dosing schedules (Start 20 mg/m^2 and increase to target dose cycle 1, week 2)
- Dose-dependent 10- or 30-min infusion. Consider up to 1 hour if patient experiences headaches
- Hydration, but do not overhydrate
- Premedication (dexamethasone and/or 5-HT3 antagonist antiemetic)
- Anticoagulation with lenalidomide (rivaroxaban or apixaban) unless contraindicated
- Monitor blood counts and response
- Monitor for infection
- Herpesvirus prophylaxis
  - » Know cardiac and pulmonary status and optimize heart failure and blood pressure management
  - » Consider baseline echocardiogram, EKG to assess left ventricular function
  - » Diuretic (furosemide or torsemide)
  - » Avoid dyspnea and side effects over the weekend: start new patient's first dose early in the week

Note. EKG = electrocardiogram. Information from NCCN (2021); Noonan et al. (2017).

Following 1 year of maintenance, Ms. B completed restaging studies. She had a negative PET/CT scan, and her bone marrow biopsy showed normal cellularity and fewer than 5% polyclonal plasma cells. Fluorescence in situ hybridization (FISH) reported no new CA, and importantly, she was noted to be minimal residual disease (MRD) negative.

Supportive Care

Infection prevention, venous thromboembolism (VTE) prophylaxis, and maintenance of bone and renal health are critical components of effective supportive care. Every agent used in the treatment of MM has a unique side effect profile that requires patient education and monitoring (Faiman, 2021). For example, patients who receive a proteasome inhibitor and/or a monoclonal antibody should receive acyclovir (there is an increased risk of reactivation of herpes zoster). Also, there is a risk of reactivation of hepatitis B virus (HBV) in patients treated with daratumumab. It is important to monitor hepatitis serologies prior to starting daratumumab and at interval time periods (Brigle et al., 2017; Burns et al., 2021). If prescribed an immunomodulatory drug, patients should be risk stratified for VTE and receive either aspirin or therapeutic anticoagulation with rivaroxaban or apixaban if there is adequate organ function (Piedra et al., 2021). Patients with MM can have a nine-fold increase in risk of developing VTE (Baljevic et al., 2022). All patients with newly diagnosed MM should receive bone-modifying therapy for at least 1 year (Terpos et al., 2021). A dental evaluation is recommended prior

to starting bone-modifying drugs to minimize the risk of osteonecrosis of the jaw (Terpos et al., 2021; Brigle et al., 2017).

Due the increased risk of VTE with carfilzomib and lenalidomide, Mrs. B began treatment with rivaroxaban 5 mg po twice daily (Piedra et al., 2021). To address her bone health, she received zoledronic acid 4 mg IV once monthly after a thorough dental evaluation and will continue this for at least 1 year.

CASE STUDY 2

Diagnosis

Mr. L was referred to oncology where he met with an AP for evaluation and workup for a probable diagnosis of multiple myeloma. Labs and imaging studies were ordered (Figure 1) to complete his workup and staging. A skeletal survey was suspicious for calvarial lesions but was otherwise negative for overt bone disease or lesions at risk of fracture. Therefore, a PET/CT was obtained per the IMWG guidelines that confirmed active osseous lesions in the bilateral humerii, femurs, and thoracic spine (Hillengass et al., 2019).

In this case, the oncology AP completed a full workup for myeloma and recommended further imaging to identify PET-avid osteolytic lesions after a negative skeletal survey. Mr. L's cardiac history and notable low serum albumin raised initial suspicion for the presence of cardiac or renal amyloidosis. However, his bone marrow biopsy was negative for amyloid on Congo red stain. Further, his serum creatinine and 24-hour urine were normal, and his echocardiogram reported no findings suggestive of amyloid infiltration. Rather, his known cardiac disease (congestive heart failure) was attributed to his long-standing hypertension.

Treatment

Following completion of the initial staging studies, Mr. L and his family met with the patient care team to discuss treatment options. Due to his cardiac status, Mr. L was not considered a good candidate for an upfront ASCT. He had excellent family support and had no issues getting transportation to clinic visits. The AP reviewed data from recent trials with Mr. L and his family and outlined several treatment options. Treatment options for newly diagnosed patients with MM are highlighted in Figure 2. The AP suggested to Mr. L and his family that it would be reasonable to consider a three-drug regimen of RVd-lite, which uses lower doses of lenalidomide, weekly SQ bortezomib, and dexamethasone in unfit patients (O'Donnell

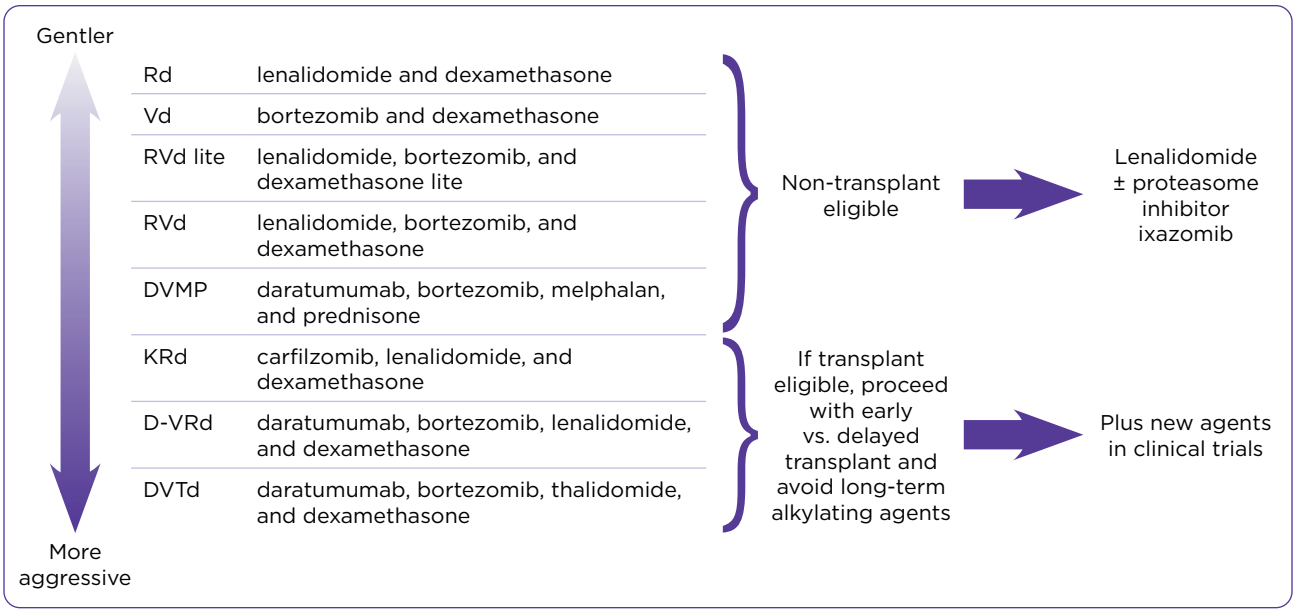

Figure 2. Treatment options for transplant eligible and ineligible patients. Consider 3–4 drug induction for all patients. For transplant eligible patients, consider upfront vs. delayed. Consider maintenance with lenalidomide with or without a proteasome inhibitor, or clinical trial. Information from Faiman & Valent (2016); NCCN (2022); Rajkumar et al. (2014).

et al., 2018). Based on Mr. L's high-risk disease status, the AP highlighted recent data to support the addition of daratumumab to the combination of lenalidomide, bortezomib, and dexamethasone (D-VRd). In the GRIFFIN study, there was a trend toward a benefit in progression-free survival at the 36-month cutoff, with rates of 88.9% (D-VRd) vs. 81.2 % (VRd). After 24 months of maintenance, 64.4% of D-VRd patients achieved MRD negativity 10^{-6} (compared with 35.8% for VRd alone; Laubach et al., 2021).

Mr. L and his family were counseled on the potential side effects related to the D-VRd regimen and signed their consent. He was enrolled on the lenalidomide Risk Evaluation and Mitigation Strategies (REMS) program and scheduled to begin treatment the following week. The reduced intensity 28-day D-VRd regimen chosen included oral lenalidomide 15 mg po × 21 days (7-day break), once weekly SQ bortezomib 1.3 mg/m^2 x 3 weeks, once weekly oral 20 mg dexamethasone, and 16 mg/kg IV daratumumab (8 weekly doses, 8 doses every other week, and then once monthly thereafter). Mr. L tolerated the first daratumumab infusion without incident and continued through the first cycle of treatment, experiencing only diarrhea that was effectively managed with over-the-counter (OTC) loperamide.

Supportive Care

Due to the presence of multiple bony lesions noted on PET scan, monthly IV infusions of zoledronic acid were recommended. As such, a referral was made to the dental clinic for evaluation and clearance. For vitamin D deficiency, twice-daily OTC calcium and vitamin D were started along with prescription vitamin D 50,000 units once weekly for 8 weeks. For thromboprophylaxis related to the lenalidomide, his current 81-mg aspirin was continued as he had no other thrombotic risk factors. For shingles prophylaxis related to the bortezomib, he began treatment with acyclovir 400 mg twice daily.

Following 8 weeks of treatment, Mr. L's myeloma markers had decreased significantly (Figure 3). Every-other-week dosing of daratumumab began following completion of the eighth weekly dose, and at that time, Mr. L was given the option of converting to SQ daratumumab (daratumumab and hyaluronidase-fihj) to decrease his time in the treatment chair. He was counselled on the potential risks, benefits and side effects of this new daratumumab formulation, and he tolerated the initial dose without incident. Following the eighth dose of every-other-week SQ daratumumab, his myeloma markers had essentially normalized, and he began monthly dosing of SQ daratumumab (Figure 3). 24 weeks into treatment, he began to experience neuropathy in his fingertips. Options to manage the neuropathy included reducing the dose of the weekly bortezomib, decreasing the frequency of bortezomib by moving to every-other-week injections, or by a combination of both interventions. Due to his high-risk cytogenetics, he was counselled on the importance of continuing the proteasome inhibitor bortezomib in lieu of omitting it altogether. He opted for a decrease in frequency (which also decreased his number of clinic visits), and thus, the bortezomib was given at the same dose but on an every-other-week schedule. His neuropathy improved over the next two cycles. To decrease the side effects related to long-term use of steroids, the dexamethasone dose was reduced from 20 mg weekly to 10 mg every other week given in combination with the bortezomib. Four months following this reduced intensity regimen, Mr. L maintained his remission.

Mr. L will continue the current regimen until progression of disease or intolerable side effects. The goal, however, will be to manage any new or existing side effects in an effort to maintain the benefit of this four-drug regimen as long as it continues to show efficacy. Depending upon the local severity of the COVID-19 pandemic, consideration will be given to change the SQ bortezomib to the oral proteasome inhibitor ixazomib to decrease his clinic visits to just once monthly. Following 1 year of treatment with monthly zoledronic acid, the frequency of the bone-targeting agent will be reduced to once every 6 months. He will continue both thromboprophylaxis and shingles prophylaxis indefinitely. Upon reaching 1 year of treatment, he will have restaging studies, including a bone marrow biopsy and repeat PET/CT scan.

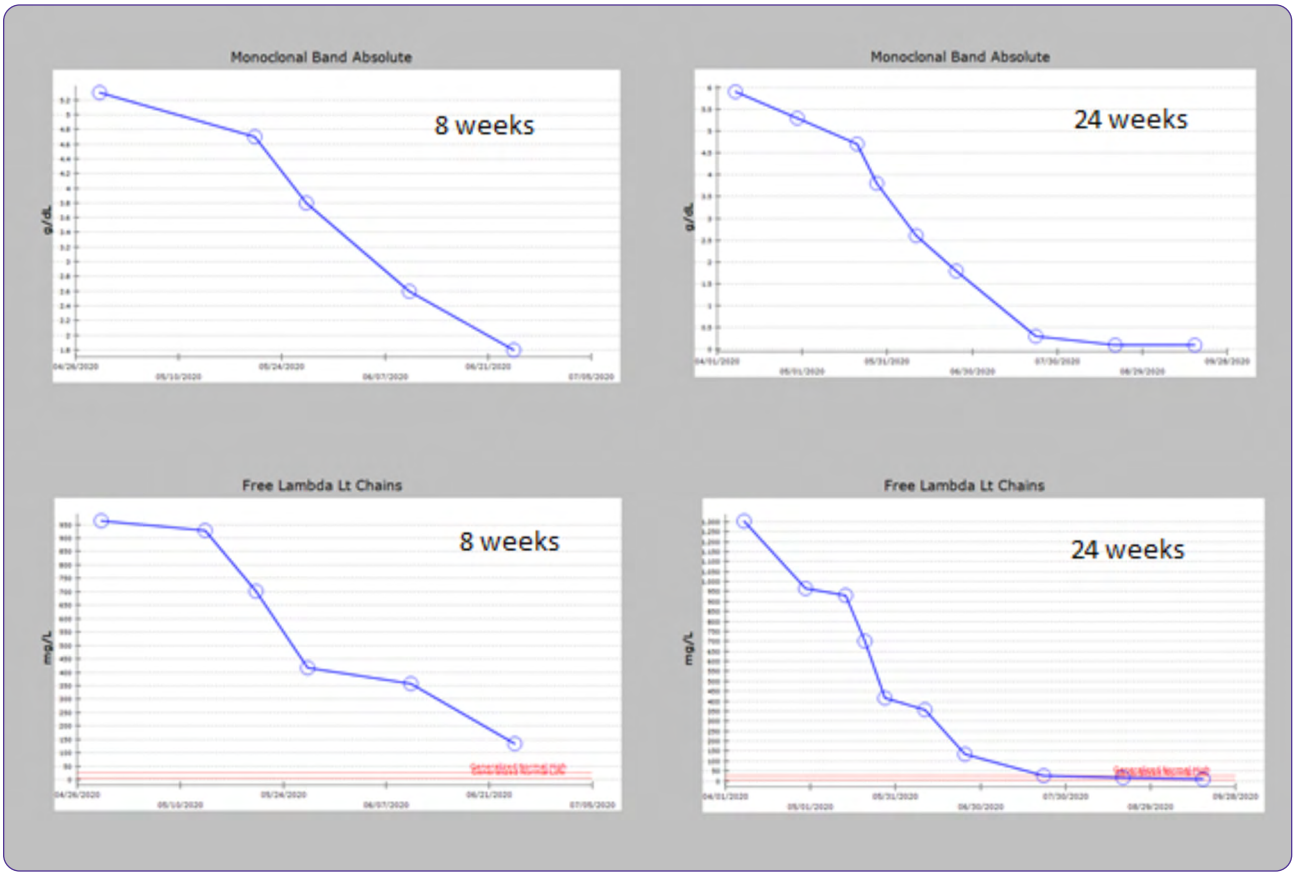

Figure 3. Monoclonal band and lambda light chain trends over the first 24 weeks of treatment. Courtesy of Kevin Brigle, PhD, ANP.

CONCLUSION

Advanced practitioners are well suited to carry out the appropriate diagnostic testing for evaluating a new diagnosis of multiple myeloma and to initiate prompt treatment in these patients. Based on the variable presentations (symptomatic vs. asymptomatic) and numerous effective initial therapies that are available, APs remain valuable members of the treatment team concerning goals of care discussions, symptom management, and treatment modifications.

Disclosure

Dr. Brigle has served on speakers bureaus for AstraZeneca, Bristol Myers Squibb, Karyopharm, Oncopeptides, and Sanofi. Dr. Verina has served on speakers bureaus for Bristol Myers Squibb, GSK, Janssen, Karyopharm, Sanofi, and Takeda. Dr. Faiman has served as a consultant for Bristol Myers Squibb, GSK, Janssen, Karyopharm, Legend Biotech, Oncopeptides, Sanofi, and Takeda.

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