# Advances in the Management of Myeloma

PRESENTED BY BETH FAIMAN, PhD, MSN, APRN-BC, AOCN®, and RACHID BAZ, MD

From Cleveland Clinic, Cleveland, Ohio; and Moffitt Cancer Center, Tampa, Florida

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

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An explosion of new agents has changed the treatment paradigm of multiple myeloma and amyloidosis. Knowledge of these drugs—their individual and class effects, including toxicity—allows advanced practitioners to keep their patients on these effective drugs, according to Rachid Baz, MD, of Moffitt Cancer Center, Tampa, and Beth Faiman, PhD, MSN, APRN-BC, AOCN®, of the Cleveland Clinic, speaking at JADPRO Live 2018.

Multiple myeloma is a cancer of the bone marrow plasma cells that is often preceded by asymptomatic monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. Today's patients often present to the clinic at the earliest end of the spectrum, even asymptomatically, the speakers noted.

Patients with MGUS do not meet the diagnostic criteria for myeloma, that is, clonal bone marrow ≥ 10% and a symptom from the "CRAB" criteria (**c**alcium elevation, **r**enal complications, **a**nemia, **b**one disease). Smoldering myeloma falls in between MGUS and active myeloma.

"In essence, MGUS and smoldering myeloma patients do not have a myeloma-defining event or damage to the body that's either present or imminent due to the plasma cell disorder," Dr. Baz said. For both categories, observation is the standard of care, although some experts believe intervention (ideally, on a clinical trial) may be appropriate for patients deemed at high risk for evolving disease. The goal is to arrest the disease before further damage occurs.

Unlike for most solid tumors, the diagnosis of multiple myeloma is a clinicopathologic one. "This means you must consider the clinical features, the lab features, and the imaging features along with the pathologic features to make a diagnosis," he said.

The revised criteria of the International Myeloma Working Group for the diagnosis of myeloma represent a paradigm shift that can impact the management of the disease (Rajkumar et al., 2014). The criteria do not solely rely on the presence of CRAB criteria, but allow, in addition, three myeloma-defining events—clonal bone marrow ≥ 60%, serum free light chain ratio > 100, and at least one focal lesion detected by MRI. Each of these markers has been associated with an approximately 80% or higher risk of developing my-

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eloma-related organ damage within 2 years, and they are sufficient for diagnosis and treatment.

"They allow you to treat a patient you are concerned about, but they don't obligate you to treat them immediately," Dr. Baz commented.

Dr. Faiman said the new approach has been helpful in her practice. "Not everyone requires treatment. I have several patients with a kappa light chain ratio > 100 that I've been watching since 2004. The criteria were set forth for you to get approval to start treatment early, if you feel it is clinically necessary." Dr. Baz added that he monitors such patients closely, and when a tumor marker rises, he initiates treatment without necessarily waiting for CRAB criteria to emerge.

For smoldering myeloma, data from the GEM-CESAR study showed a benefit of early intervention in patients deemed at high risk (Mateos et al., 2017). Aggressive treatment with carfilzomib, lenalidomide, and dexamethasone, followed by transplant or consolidation, led to a progression-free survival of 94% at 28 months and a 62% rate of minimal residual disease (MRD) negativity. The long-term outcomes are awaited for this "work in progress," Dr. Baz said. A new approach in smoldering myeloma involves single-agent daratumumab (Darzalex), based on CENTAURUS data showing that long intensive treatment (up to 20 weeks) yielded a 93% progression-free survival rate at 24 months (Hofmeister et al., 2017).

In brief, early treatment of smoldering myeloma possibly confers a survival benefit, potentially delays or prevents irreversible complications, and is reasonably well tolerated. But not all patients require an aggressive approach that is financially costly and carries the potential for late toxicities, he maintained. "There are reasons why the standard of care for smoldering myeloma remains observation: some patients may never require therapy," he concluded.

## MEASURING MINIMAL RESIDUAL DISEASE

It is now possible to look for disease that remains after treatment to the level of one cell in a million in the bone marrow. The lack of MRD (i.e., MRD negativity) has been associated with better outcomes, but MRD detection also has pitfalls and MRD negativity does not indicate curable disease. "If I have a patient in a complete response for 11 years on lenalidomide (Revlimid) maintenance, if he or she is MRD-negative, it does not mean I will take him off treatment," Dr. Faiman noted.

While detecting and monitoring MRD is proving to be a useful tool for clinical trials, and tests are available and reimbursable, it is not ready for clinical use, Dr. Baz and Dr. Faiman agreed. "We're starting to test for this, but not yet in a way that affects decision-making," Dr. Baz said. "We don't know yet how to best target MRD in terms of decision-making."

## INITIATING TREATMENT

The current regimen for most newly diagnosed patients is a triplet (mostly, bortezomib [Velcade], lenalidomide, dexamethasone), followed by consolidation with high-dose melphalan and autologous stem cell transplant, followed by maintenance therapy (or observation). For relapsed disease, there are numerous options and no one standard of care.

As more combinations come to the clinic, practitioners should be aware of side effects of each agent (Table 1), Dr. Faiman emphasized. "When starting treatment, research the common side effects and think about whether there are overlapping toxicities," she advised.

Frailty predicts outcomes from myeloma treatment more powerfully than any other factor, but age should be viewed as a continuum. "The setting where you most need to look for frailty is ages 70 to 75, where the patient might be frail and you are not sure," he said. The Geriatric Assessment and Frailty index can be useful in this assessment (myelomafrailtyscorecalculator.net).

### Induction Regimens in Newly Diagnosed Patients

The SWOG S0777 trial established a three-drug regimen as the preferred induction regimen over a two-drug regimen in transplant-eligible patients. Six months of lenalidomide/dexamethasone plus bortezomib (VRd; followed by maintenance Rd) led to a median progression-free survival of 43 months vs. 30 months for Rd alone (hazard ratio [HR], 0.712; $p$ = .0018), with an 11-month survival advantage also shown (HR, 0.71; $p$ = 0.25; Durie et al., 2017). "This improvement came at the cost

**Table 1. Side Effects of Common Myeloma Drugs**

| | Thalidomide | Lenalidomide | Pomalidomide | Bortezomib | Carfilzomib | Ixazomib | Panobinostat | Elotuzumab | Daratumumab |
|---|---|---|---|---|---|---|---|---|---|
| Peripheral neuropathy | ✓ | | | ✓[a] | | ✓ | | | |
| Thrombosis (DVT, PE) | ✓ more with dex | ✓ more with dex | ✓ more with dex | | ✓ | | | | |
| Myelo-suppression | ✓ neutro | ✓anemia, thrombo, neutro | ✓ neutro, anemia, thrombo | ✓ thrombo | ✓ neutro, thrombo | ✓ thrombo | ✓ neutro, thrombo | | ✓ neutro, thrombo |
| Cardio-pulmonary | ✓ slow heart rate | ✓ slow heart rate | ✓ shortness of breath | ✓ hypotension | ✓ shortness of breath, other | | ✓ QT↑, arrhythmias, ischemia | | |
| Fatigue, weakness | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sedation | ✓ | | | | | | | | |
| Rash | ✓ | ✓ | ✓ | | | ✓ | | | |
| GI disturbance | ✓ constipation | ✓ diarrhea, constipation | ✓ diarrhea, constipation | ✓ nausea, vomiting, diarrhea | ✓ nausea, vomiting, diarrhea, constipation | ✓ nausea, vomiting, diarrhea | ✓ diarrhea, nausea, vomiting | ✓ diarrhea, nausea | ✓ diarrhea |
| VZV | | | | ✓ | ✓ | ✓ | | | |
| Infusion reaction | | | | | | | | ✓ ~10% | ✓ ~40% |

*Note.* DVT = deep vein thrombosis; PE = pulmonary embolism; dex = dexamethasone; neutro = neutropenia (low white blood cell) count; thrombo = thrombocytopenia (low platelets); GI = gastrointestinal; VZV = varicella zoster virus. Information from Amgen (2018); Bristol-Myers Squibb Company (2018); Celgene Corporation (2017, 2018a, 2018b); Janssen Biotech, Inc. (2018); Millennium Pharmaceuticals, Inc. (2017); Novartis (2016).
[a]Subcutaneous or weekly administration of bortezomib reduces risk of peripheral neuropathy.

of toxicity, and we now realize there may be better ways to give bortezomib (i.e., subcutaneously). Nonetheless, the study was very compelling and it has consolidated VRd as the standard of care for newly diagnosed myeloma," he said.

With effective new agents, is transplant still necessary? The IFM 2009 Study evaluated autologous stem cell transplant (ASCT) vs. no ASCT after VRd induction, followed by maintenance lenalidomide (Attal et al., 2017). Median progression-free survival was 50 months with ASCT and 36 months with VRd alone (at higher doses; $p < .001$), but 4-year survival was 81% and 82%, respectively. The findings suggest there is a benefit from transplant, but patients who defer ASCT until later will not compromise survival.

Dr. Baz emphasized the importance of maintenance, which is most often with lenalidomide, although ixazomib (Ninlaro) and lenalidomide in combination with new agents can also be considered in some patients. Since myeloma is a clonal disease, and clones change over time, ongoing treatment is needed to suppress these clones. Dr. Faiman added that, during maintenance, it is important to monitor for disease activity and changes in baseline disease characteristics.

## TREATMENT SELECTION AT RELAPSE

Many new drugs are available for relapsed disease. Shared decision-making about treatment should be guided by efficacy data, disease-related characteristics and comorbid conditions, treatment-related factors (such as previous therapy and cost), and patient preferences, Dr. Faiman said.

To Dr. Baz, the approach to relapse is "more an art form than a science." In fact, he noted, not all patients in relapse even require treatment. For patients with low-risk disease features, a slight manipulation to treatment may be sufficient. "If a patient is on lenalidomide maintenance, for example, we may just add back steroids." On the other hand, signs of aggressive relapsed disease—such as a sudden rise in light chain, with symptoms—warrant aggressive combinations.

"Among the many options for relapsed/refractory myeloma, we try to find medicines the patient has not been exposed to and is likely to tolerate well. In early relapse, we can be a bit picky in terms of convenience and preference, but with late relapse we're more limited," he said.

The proteasome inhibitor carfilzomib (Kyprolis) plus lenalidomide/dexamethasone (KRd) yielded an overall survival of 73% at 24 months in the ASPIRE trial (Stewart et al., 2015). Subsequent to this, the ARROW study demonstrated that once-weekly 20/70 mg/m$^2$ carfilzomib yielded better outcomes, with more convenience and no increase in cardiac toxicity over the standard 20/27 mg/m$^2$ twice weekly (Mateos et al., 2018). The oral proteasome inhibitor ixazomib (plus Rd), taken just three times a month, is an attractive choice for many patients, according to Dr. Faiman.

Pomalidomide (Pomalyst) is FDA-approved as a single agent and in combination with carfilzomib and daratumumab "but can be given with just about everything," Dr. Faiman indicated. The main considerations for this and other immunomodulatory drugs is deep vein thrombosis; patients on these drugs should be on daily aspirin or an anticoagulant and should stay well hydrated, she added.

The monoclonal antibodies are also effective additions to Rd. Elotuzumab (Empliciti) improved progression-free survival in the ELOQUENT-2 trial (Lonial et al., 2015). Daratumumab proved beneficial in various combination regimens in a number of trials (Dimopoulos et al., 2016; Khouri et al., 2017; Palumbo et al., 2016).

## PROTECTING THE BONE

The speakers emphasized the importance of giving bone-modifying agents to reduce skeletal-related events, as recommended in recent ASCO guidelines (Anderson et al., 2018). Dr. Baz prescribes either zoledronic acid or denosumab, giving monthly therapy to patients with bone disease at diagnosis and every-3-month therapy to those without bone disease at presentation. After transplant, patients may be treated every 3, 6, or even 12 months if they remain in complete remission for that long.

## AMYLOIDOSIS: WHEN TO SUSPECT AND TEST

The most common form of amyloidosis treated in oncology is AL amyloidosis. This refers to the deposition of protein derived from immunoglobulin

light chain fragments. Virtually all patients have detectable M protein or serum free light chains. The key to diagnosis is a high index of suspicion.

"About 10% of myeloma patients will also have amyloidosis and I do screen for it," Dr. Baz said. "I obtain an NT-proBNP (N-terminal pro b-type natriuretic peptide) and troponin for all patients who come to our plasma cell disorder clinic."

Symptoms can be related to the heart (congestive heart failure, palpitations, arrhythmias), nerves (numbness, weakness, autonomic sensations), kidney (swelling, foamy urine), and skin (easy bruising, bleeding or tongue enlargement, a late manifestation). Amyloidosis should be suspected in the patient who has nephrotic syndrome or neuropathy without diabetes, nonischemic restrictive cardiomyopathy, or an atypical myeloma presentation, he said. Other clues are an echocardiogram showing enlarged septum, sparkling appearance, and/or low voltage on the electrocardiogram. On the other hand, cardiac manifestations may be minor or absent. Heart involvement heralds a worse prognosis. Early diagnosis is important, and many tests are needed to confirm this (Table 2).

## Treatment of Amyloidosis

Treatment addresses the underlying plasma cell disorder and is aimed at preventing complications and further organ damage. Conventional management is with agents used in myeloma. In some centers, transplant is the primary approach, but the majority of patients are not candidates. Daratumumab was recently reported to be very effective, perhaps more so in amyloidosis than in myeloma (Khouri et al., 2017; Roussel et al., 2017; Sanchorawala et al., 2017).

Finally, Dr. Faiman emphasized that for all plasma cell dyscrasias, a collaborative approach is key to good management. This includes the oncologist, advanced practitioner, nursing support services, consultants, caregivers, and at the center, the patient.

## Disclosure

Dr. Faiman has acted as a consultant and/or served on the speakers bureau for Amgen, Celgene, Janssen, and Takeda. Dr. Baz has received research honoraria from Celgene and research support from AbbVie, Bristol-Myers Squibb, Celgene, Karyopharm, Merck, and Takeda.

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**Table 2. Tests Suggested for the Diagnosis and Monitoring of Primary (AL) Amyloidosis[a]**

- SPEP, UPEP
- $ß_2$M, CBC diff, CMP, ALB
- Monoclonal protein, blood and urine
- 24-hr urine for protein
- Skeletal survey to r/o lesions
- High sensitivity TNT assay: improves detection of cardiac involvement and powerful diagnostic determinant
- Serum free light chain assay: more sensitive for organ response
- Echocardiography, fat-pad aspirate "congo red stain"
- Thioflavin if endomyocardial biopsy

*Note.* MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; $ß_2$M = beta-2-microglobulin; CBC = complete blood count; CMP = comprehensive metabolic panel; ALB = albumin; r/o = rule out; TNT = troponin T.
[a]Some have systemic MM as well as AL amyloid.

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