LETTER FROM THE EDITOR-IN-CHIEF

Over the past several years, significant progress has been made in the management of multiple myeloma (MM). This is due, in large part, to an accumulating knowledge of the biology of the disease, along with the development and clinical investigation of highly effective therapies. The shift in the paradigm of care for MM has resulted in revised criteria for diagnosing, staging, and risk-stratifying patients; new standards of care; and updated guidelines for the management of comorbidities and treatment-related toxicities. However, more progress is needed and many questions remain regarding the application and interpretation of recent clinical advances.

In this fifth annual “Considerations in Multiple Myeloma” newsletter series, we continue to address frequently asked questions related to the diagnosis and treatment of the disease. To provide an interprofessional perspective, questions are answered by physicians, nurses, and pharmacists from leading cancer institutions, who share their insight, knowledge, and professional experience regarding evidence-based care. In this first issue, experts from Winship Cancer Institute of Emory University answer questions pertaining to the management of newly diagnosed patients.

Sincerely,

Sagar Lonial, MD
Professor
Vice Chair of Clinical Affairs
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Emory University School of Medicine
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CONSIDERATIONS IN MULTIPLE MYELOMA

What criteria are used to distinguish smoldering multiple myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS) from active myeloma?

MGUS and SMM are asymptomatic, and each carries a considerably different potential for progression to MM. Patients with MGUS have <3 g/dL monoclonal (M) protein in serum and <10% of bone marrow plasma cells (BMPCs), but they do not have end-organ damage. In SMM, the clinical and laboratory findings are the same as MGUS except that the serum M-protein is ≥3 g/dL and/or the BMPCs are ≥10%. Symptomatic MM is determined by the presence of ≥10% BMPCs, serum or urinary M-protein, and evidence of end-organ damage; specifically, hypercalcemia, renal insufficiency, anemia, or bone lesions (Table 1).  

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Evolving Concepts in the Management of Newly Diagnosed Multiple Myeloma

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Table 1. Diagnostic Criteria for Specific Plasma Cell Disorders

<table>
<thead>
<tr>
<th>Plasma Cell Disorder</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma (MM)</td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>• Serum monoclonal protein &lt;3 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Bone marrow plasma cells &gt;10%</td>
</tr>
<tr>
<td></td>
<td>• Evidence of end-organ damage that can be attributed to the plasma cell proliferative disorder</td>
</tr>
<tr>
<td>Smoldering multiple myeloma (SMM)</td>
<td>(also referred to as asymptomatic multiple myeloma)</td>
</tr>
<tr>
<td></td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>• Serum monoclonal protein (IgG or IgA) &gt;3 g/dL and/or clonal bone marrow plasma cells &gt;10%</td>
</tr>
<tr>
<td></td>
<td>• Evidence of end-organ damage (such as CRAB criteria) that can be attributed to the plasma cell proliferative disorder</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS)</td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>• Serum monoclonal protein &lt;3 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Bone marrow plasma cells &gt;10%</td>
</tr>
<tr>
<td></td>
<td>• Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder (specifically CRAB): Calcium elevation: serum calcium ≥11.5 mg/dL or Renal insufficiency: serum creatinine &gt;2 mg/dL Anemia: hemoglobin &gt;2 g/dL below lower limit of normal or value &lt;10 g/dL Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures</td>
</tr>
</tbody>
</table>

How have staging criteria for MM evolved over time?

First published in 1975, the Durie-Salmon (DS) staging system was the method clinicians commonly relied on for staging MM for more than 25 years. This system assessed myeloma tumor burden, and based stages I, II, and III on serum M-spike, hemoglobin, calcium level, and number of bone lesions. Subclassifications A and B reflected the degree of kidney involvement, as measured by creatinine level. The DS staging system provided a framework by which clinicians could communicate clearly with each other regarding the extent of the disease. Unfortunately, there were drawbacks to this system. Many found it to be too complex, and there were problems in terms of evaluating lytic bone lesions accurately. To address these issues, investigators proposed a new method of staging called the International Staging System (ISS). This system includes an assessment of beta-2-microglobulin (ß2M) and serum albumin levels, which were shown in a multi-variant analysis to be the 2 important prognostic factors in myeloma. Patients with stage I disease have a ß2M level <3.5 mg/L and albumin level ≥3.5 g/dL (median survival 62 months) compared with stage III with ß2M ≥5.5 mg/L (median survival 29 months) and stage II (not meeting criteria for either stage I or III) (median survival 44 months). Because ß2M and serum albumin are easily obtainable parameters, the ISS has superseded the DS staging system and is now widely accepted as the standard of care for staging MM.

What role does cytogenetic testing play in the prognosis and treatment of newly diagnosed patients with MM?

The use of cytogenetic testing to help identify myeloma patients with high-risk disease continues to evolve as we learn more about the biology of the disease. Conventional metaphase karyotyping is one modality for assessing risk, but it is not as informative as we would like because myeloma cells proliferate poorly in vitro. This method of analysis is useful, however, for the screening of hyper- and hypodiploidy and cytogenetic abnormalities such as deletion of chromosome 13 [del(13q)]. Fluorescence in situ hybridization (FISH), on the other hand, analyses cells in mitotic interphase, which allows better identification of certain chromosomal abnormalities. In particular, it is instrumental in screening for del(13q), deletion of the short arm of chromosome 17 [del(17p)], translocations involving chromosomes 4, 11, 14, and 16 [t(4;14), t(11;14), and t(14;16)], and IgA subclassification. Abnormalities indicative of poorer prognosis in myeloma include del(17p), t(4;14), and t(14;16). Interestingly, del(13q), once considered a high-risk characteristic, is no longer thought to indicate a poor prognosis if it occurs independently of other cytogenetic abnormalities.

At diagnosis, metaphase karyotyping and FISH results are certainly very important to obtain and use in treatment planning, but they must be considered in the context of other features of a patient’s condition, such as age, stage of disease, extent of bone disease and renal function, and comorbidities. In addition, there is still a question as to how best to incorporate results into a patient’s course of therapy because cytogenetic abnormalities continue to evolve over time. At our institution, we retest cytogenetics prior to transplantation to determine whether a patient’s risk status has changed in any way. Clinical evidence suggests that bortezomib and lenalidomide may have particular value in the context of certain high-risk cytogenetics. Whenever possible, we treat newly diagnosed myeloma patients with regimens that contain one or both of these agents.

In addition to cytogenetic abnormalities, gene expression profiling (GEP) signatures are now being identified, including a 70-gene profile from the...
University of Arkansas and a 15-gene profile by the Intergroupe Francophone du Myélome. Although these 2 profiles do not share any common genes, GEP has the potential to be a useful tool for risk-stratifying patients and determining optimal therapy, and investigation in this area continues. For example, GEP signatures are being utilized in the ECOG E1A06 trial for SMM, to help identify patients who are going to have higher or lower risk of progression.

How do you determine the appropriate treatment for newly diagnosed MM?

For transplant-eligible patients, the approach we typically use is frontline treatment with a combination of lenalidomide, bortezomib, and dexamethasone (RVD). In a phase 1/2 study in newly diagnosed patients, this combination was shown to have favorable tolerability, and resulted in a partial response or better rate of 100%, with a 74% rate of very good partial response or better in the phase 2 population (Figure). The study included subgroup analyses of patients with high-risk cytogenetics, which showed that response to RVD was unaffected by cytogenetic abnormalities. This finding suggested that RVD may overcome high-risk cytogenetics, but was not definitive because of the small sample size of patients with these abnormalities. We almost always use this combination, whether the risk is standard or high, unless the patient has plasma cell leukemia or another medical condition that would require a different approach to treatment.

RVD is also being used more frequently in the nontransplant setting, as long as patients can tolerate these agents. If RVD is too aggressive, we consider regimens using melphalan and prednisone combined one of the novel agents bortezomib, lenalidomide, orthalidomide. If we can find a clinical trial that would suit the needs of transplant-ineligible patients better, we may offer that to them.

What advances have been made to help clinicians assess bone disease in MM?

In the most recent consensus guidelines from the International Myeloma Working Group, the bone survey is still the gold standard for assessing myeloma bone disease. However, there is a movement among many cancer centers to make more frequent use of MRI and positron emission tomography/computed tomography (PET/CT) scans. Fortunately, Medicare now allows coverage of PET/CT scans for myeloma. At our institution, we consider each patient’s case on an individual basis. In general, we still conduct a bone survey. If results are negative, we will typically do an MRI of the spine and pelvis, as this procedure can pick up abnormalities even if a plain film is negative in symptomatic patients. The use of PET scans is clearly important, because they can detect not only bone-based disease, but also extramedullary disease.

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For patients with oligosecretory or nonsecretory disease who do not have laboratory parameters to monitor outside of a bone marrow examination, and particularly for patients with extramedullary plasmacytomas, we use PET scans to monitor them and to document whether they are in remission. We also repeat bone assessments by PET or MRI after a course of therapy. For transplant-eligible patients, this is done prior to transplant to document the degree of response to treatment. For transplant-ineligible patients, this practice helps us to determine whether we should continue with the current approach to therapy.

Conclusion

Progress in the diagnosis and treatment of MM has been tremendous over the past 10 to 15 years and continues to move forward. We are going to continue to see new drugs come along that will not doubt result in even more progress. In this last decade alone, we have been able to take the novel agents thalidomide, lenalidomide, and bortezomib, and utilize them in numerous combinations and schedules. In addition to the continued research to find an approach to cure, I think the future of myeloma may be in going back to the precursor diseases. I believe MGUS and SMM are where we are ultimately going to learn why these plasma cell dyscrasias progress to myeloma.

References
7. Lenalidomide or observation in treating patients with asymptomatic high-risk smoldering multiple myeloma. 

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Improving Patient Outcomes in Newly Diagnosed Multiple Myeloma

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Oncology Certified Registered Nurse/Multiple Myeloma Team/BMT
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Introduction
At the time of diagnosis, patients with multiple myeloma (MM) may present with numerous disease-related symptoms. Each of these complications requires supportive care, and providing that care demands a high degree of individualization. In many cases, one symptom can influence the management of another. For example, renal insufficiency may impact the administration of bisphosphonates used to protect bone health. In addition, specific agents used to treat myeloma may produce confounding symptoms, such as neurotoxicity in a patient already experiencing disease-related bone pain. In this article, Melanie Watson, RN, OCN, discusses her center’s evidence-based approach to providing symptom relief for patients with newly diagnosed myeloma.

What is the nurse’s role in the assessment and management of patients with MM who present with hypercalcemia?

Elevated calcium is a relatively common laboratory finding in patients newly diagnosed with MM (Figure). The incidence of hypercalcemia—defined as a very high serum calcium (≥11 mg/dL)—is approximately 13%; however, an additional 15% of patients present with calcium levels of 10.2 to 10.9 mg/dL. When we conduct an initial work-up on a patient, a finding of hypercalcemia prompts us to take necessary steps to minimize this complication. Intervention becomes especially urgent if the patient reports potential symptoms of hypercalcemia, such as emesis, weakness, and confusion. Immediate hydration is essential, and many patients will also require bisphosphonate therapy. In some instances, it is necessary to prescribe antiemetic agents for patients who are experiencing hypercalcemia-related nausea and vomiting.

At our center, we treat hypercalcemia if the serum calcium level is ≥10.5 mg/dL. We also initiate treatment if serum calcium is only borderline high, but serum albumin is low, as the serum calcium should be corrected based on the serum albumin. Some patients present with very mild hypercalcemia (10.5 mg/dL with a low albumin); our approach with these patients is to treat with intravenous (IV) hydration only, and then routinely check their calcium levels. For all other patients, we control hypercalcemia with hydration plus bisphosphonate therapy (zoledronic acid or pamidronate). If zoledronic acid is used, it is given as a single IV dose of 4 mg infused over 15 to 30 minutes. This is followed by a second 4-mg dose given at a minimum of 7 days, if necessary. Pamidronate dosing of 60 mg to 90 mg, infused over 2 to 4 hours, is dependent on the level of albumin-corrected serum calcium as well as a patient’s renal function. Treatment with bisphosphonate therapy generally results in rapid resolution of hypercalcemia.

Renal insufficiency is also prevalent in newly diagnosed patients with MM. What role do nurses play in the evaluation, monitoring, and supportive care of this complication?

Approximately 19% of patients with MM present with a serum creatinine ≥2 mg/dL at the time of diagnosis (Figure). Renal dysfunction may be exacerbated by hypercalcemia, but even after serum calcium levels have stabilized, we still have to contend with myeloma-related renal tubular pathology. The presence of renal insufficiency sometimes signals that the patient has light-chain myeloma, which has been correlated with elevated creatinine.

Circulating monoclonal immunoglobulin free light chains can clog up renal tubules; myeloma kidney is characterized by light-chain cast nephropathy. Laboratory testing for serum creatinine, creatinine clearance, and serum and urine protein electrophoresis are critical in the initial work-up of patients with MM. Nurses are primarily responsible for the evaluation of any symptom patterns related to impaired renal function, such as elevated blood pressure, changes in urination, and fatigue. It is important to remember, however, that a patient may have renal insufficiency in the absence of any physical signs or symptoms. Following initial assessment, we keep a close watch on renal function and check laboratory results at every visit, which during frontline treatment may be several times a week. We also encourage patients to drink between 2 and 3 L of fluid a day to stay hydrated.

It is imperative to obtain a list of every drug the patient is taking, to ensure that none of them are renally toxic—this includes over-the-counter (OTC) medications. We strongly advise patients to avoid the use of OTC or prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), which can have adverse renal effects. We also remind them to report any changes in their urine (eg, output, frequency, appearance, presence of blood).

Figure. Incidence of anemia, renal dysfunction, and hypercalcemia in newly diagnosed patients with MM (N=1027).

<table>
<thead>
<tr>
<th>Hemoglobin ≤10 g/dL</th>
<th>Creatinine ≥2 mg/dL</th>
<th>Calcium ≥11 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>35%</td>
<td>19%</td>
<td>13%</td>
</tr>
</tbody>
</table>

MM indicates multiple myeloma.
A small subset of patients with myeloma-related renal insufficiency will require dialysis. In many cases, this need for dialysis is reversible with effective antmyeloma treatment. Reducing the myeloma burden as quickly as possible is the key to getting patients off dialysis. Our induction therapy for newly diagnosed patients with significant renal dysfunction—certainly in the transplant-eligible group but also in many nontransplant candidates—is the combination of bortezomib, thalidomide, and dexamethasone (VTD). The inclusion of novel agents in this regimen offers a benefit to therapy to protect against skeletal-related events (SREs), since this class of drugs is excreted via the kidney and can therefore produce renal toxicity. At our institution, we use zoledronic acid for patients with a baseline creatinine clearance of ≥30 mL/min, dose-adjusted as creatinine clearances from >60 mL/min to 30 mL/min. This is given as a 30-minute infusion, which, in our experience, tends to be gentler on the kidney than the standard 15-minute infusion. If creatinine clearance is below 30 mL/min we use pamidronate, although the pharmacokinetic data on its use in such instances is limited.

In addition to initiating bisphosphonate therapy, what other supportive care strategies are necessary for patients with myeloma-related bone disease?

Table 1. Suggested Lenalidomide Dose Reductions for Renal Impairment

<table>
<thead>
<tr>
<th>Degree of Renal Dysfunction</th>
<th>Renal Function (Cockcroft-Gault CrCl)</th>
<th>Dose for MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>30-60 mL/min</td>
<td>10 mg orally every 24 hours</td>
</tr>
<tr>
<td>Severe (not requiring dialysis)</td>
<td>&lt;30 mL/min</td>
<td>15 mg orally every 48 hours</td>
</tr>
</tbody>
</table>
| End-stage renal disease (requiring dialysis) | <30 mL/min | 5 mg orally once daily

CrCl indicates creatinine clearance; MM, multiple myeloma.

Table 2. Bortezomib Dose Modifications Based on Severity of Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy</th>
<th>Modification of Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia or loss of function) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 (interferes with function but not with activities of daily living)</td>
<td>Reduce bortezomib dose from 1.3 to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interferes with activities of daily living)</td>
<td>Withhold bortezomib until toxicity resolves, then reinstitute at a dose of 0.7 mg/m² once weekly</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss that interferes with function)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

Grading based on NCI Common Toxicity Criteria CTCAE V 3.0.

The severity of renal impairment affects our selection of bisphosphonate therapy to protect against skeletal-related events.

The severity of renal impairment affects our selection of bisphosphonate therapy to protect against skeletal-related events (SREs), since this class of drugs is excreted via the kidney and can therefore produce renal toxicity. At our institution, we use zoledronic acid for patients with a baseline creatinine clearance of ≥30 mL/min, dose-adjusted as creatinine clearances from >60 mL/min to 30 mL/min. This is given as a 30-minute infusion, which, in our experience, tends to be gentler on the kidney than the standard 15-minute infusion. If creatinine clearance is below 30 mL/min we use pamidronate, although the pharmacokinetic data on its use in such instances is limited.

In addition to initiating bisphosphonate therapy, what other supportive care strategies are necessary for patients with myeloma-related bone disease?

Approximately 80% of patients with MM present with SREs, which typically manifest as osteolytic lesions or fractures. Therefore, bisphosphonate therapy is a mainstay of bone support in MM. From a nursing perspective, ongoing patient education about bisphosphonate use is critical to help patients remain on this effective therapy. The most important educational intervention is in the area of dental hygiene, since osteonecrosis of the jaw (ONJ) is a rare but very serious adverse effect of bisphosphonate therapy, for which there is no satisfactory intervention. For example, zoledronic acid was shown in the Medical Research Council Myeloma IX study to reduce SREs and improve overall survival compared with clodronic acid, but it also produced a higher rate of ONJ than clodronic acid.

We require a dental exam before we start a bisphosphonate for SRE prevention. We repeatedly inform patients that they should have no invasive dental procedures that disturb the bone while being treated with bisphosphonates. We tell patients, “If it’s above the gum line, it’s fine. If it’s below the gum line, it’s not.” If an invasive procedure becomes necessary, we need to know in advance. We hold the bisphosphonate therapy for 2 months before and 2 months after any invasive dental procedure.

Treatment of bone pain is another critical aspect of supportive care. Nurses have always held a leadership role in the management of pain, and it takes all of our skill and insight to effectively treat the complexities of
CONTINUING EDUCATION

We rarely use erythropoietins to treat anemia, as most of our patients are receiving therapies that may elevate risk of thrombosis, such as thalidomide or lenalidomide, combined with dexamethasone. In addition, erythropoietins can increase thromboembolic risk. We therefore do not want to augment risk of thrombosis by adding an erythropoietin to the mix. In rare instances, we may opt for erythropoietin support of anemia in heavily treated patients who are far into the clinical course and have already received multiple transfusions and anticoagulant therapy. It is important to provide ongoing education to patients regarding the signs and symptoms of anemia, which can include shortness of breath or extreme fatigue. We describe how hemoglobin in red blood cells carries oxygen throughout the body, so that they understand why we must frequently check their counts and recommend transfusions. Patients often call us and say, “I’ve been extremely tired over the past couple of days. I wonder if I need a transfusion.” When this occurs, we have them come in to the clinic so that we can assess their blood cell counts, and we often find that these patients are correct and do need to be transfused.

To be effective in providing prompt and appropriate supportive care, nurses must listen attentively to their patients’ concerns. Most patients can sense subtle changes in their bodies, and our education is designed to contribute to that knowledge. As a nurse, I feel I have done my job well when a patient demonstrates an understanding of their disease and feels comfortable calling me to report a new symptom or potential complication.

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Opioid treatment is often necessary for myeloma-associated bone pain, which was reported by 58% of patients at the time of diagnosis in one study. Since we cannot prescribe NSAIDs to myeloma patients, we rely on opioid analgesics to control pain. When we give these medications, we always put patients on a bowel regimen that includes dietary and hydration support and a stool softener, as opioids can cause significant constipation. We try not to use radiation therapy for pain; we only radiate for severe pain that has not responded to other interventions, including analgesic medication, physical therapy (PT), and surgery. Patients sometimes do not understand why PT can help with bone pain, so we explain that improving muscle strength around a bone may improve pain control and function.

Compression fracture of the spine is one of the more common SREs in myeloma patients. In our weekly clinic, a spine specialist is available to evaluate individuals with back pain. If necessary, patients may undergo kyphoplasty, which has been shown to be effective in treating vertebral compression fractures in patients with MM or bone metastasis from solid tumors (Table 3). The specialist may also recommend a steroid injection into the back to relieve the pain. Finally, we advise patients to take the necessary steps to protect themselves from trauma. The last thing they need is an injury to bone. We urge them to avoid risky sports and counsel them to evaluate their homes for hazards such as slippery rugs and broken steps.

What supportive care strategies are necessary for managing anemia in patients with MM?

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What supportive care strategies are necessary for managing anemia in patients with MM?

Anemia is a common finding among newly diagnosed MM patients (Figure). This condition may also occur at later points in the clinical course of the disease and can be an adverse effect of specific agents. We take a dual approach to combat anemia, using effective antimyeloma therapy and transfusions. Controlling a patient’s disease is the best way to manage anemia over the long term. We order blood transfusions whenever a patient’s hematocrit drops to about 25% to 27%. Hematocrit ≤25% signals that a transfusion is appropriate; 26% to 27%, in the presence of anemia symptoms, also indicates a need for transfusion.

We rarely use erythropoietins to treat anemia, as most of our patients are receiving therapies that may elevate risk of thrombosis, such as thalidomide or lenalidomide, combined with dexamethasone. In addition, erythropoietins can increase thromboembolic risk. We therefore do not want to augment risk of thrombosis by adding an erythropoietin to the mix. In rare instances, we may opt for erythropoietin support of anemia in heavily treated patients who are far into the clinical course and have already received multiple transfusions and anticoagulant therapy. It is important to provide ongoing education to patients regarding the signs and symptoms of anemia, which can include shortness of breath or extreme fatigue. We describe how hemoglobin in red blood cells carries oxygen throughout the body, so that they understand why we must frequently check their counts and recommend transfusions. Patients often call us and say, “I’ve been extremely tired over the past couple of days. I wonder if I need a transfusion.” When this occurs, we have them come in to the clinic so that we can assess their blood cell counts, and we often find that these patients are correct and do need to be transfused.

To be effective in providing prompt and appropriate supportive care, nurses must listen attentively to their patients’ concerns. Most patients can sense subtle changes in their bodies, and our education is designed to contribute to that knowledge. As a nurse, I feel I have done my job well when a patient demonstrates an understanding of their disease and feels comfortable calling me to report a new symptom or potential complication. Good communication between nurses and patients is the cornerstone for providing the best possible supportive care.

Conclusion

MM is an incurable hematologic malignancy that attacks the body in many ways, resulting in renal dysfunction, hypercalcemia, SREs, and anemia. It is imperative that patients are carefully screened for these complications at the time of diagnosis and throughout the course of the disease. Proactive nursing measures are the key to reducing the impact and severity of these symptoms, which in turn will help patients remain on therapy and achieve the best possible outcomes.

References

Pharmacologic Considerations in Newly Diagnosed Multiple Myeloma

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Introduction

Symptomatic MM is defined by the presence of CRAB symptoms, which identify end-organ involvement. As a pharmacy professional, what is your role in minimizing these symptoms in newly diagnosed patients?

Our priority as pharmacists is to counsel patients regarding their treatment regimen and assess the interaction of agents, whether it be with other drugs or with a patient’s comorbid conditions. When a patient newly diagnosed with MM presents with CRAB symptoms, we evaluate the drugs he or she takes for preexisting conditions in the context of the proposed treatment regimen, in an effort to discover and manage any problematic interactions. For example, a newly diagnosed, elderly woman may present with renal insufficiency and bone lesions attributable to MM, but may also have a history of diabetes, controlled with oral metformin, and osteoporosis treated with the oral bisphosphonate, ibandronate. Oral ibandronate and metformin do not interact. However, the risk of lactic acidosis, a rare but serious complication of metformin, is elevated in patients with renal insufficiency and older age. Antimyeloma regimens that include steroids such as dexamethasone or prednisone may interfere with glycemic control. Intravenous (IV) bisphosphonate therapy for MM should replace oral ibandronate; if the patient’s creatinine clearance is <30 mL/min, IV pamidronate rather than IV zoledronic acid would be the recommended agent.

It is important to stress that medication therapy management provided by a pharmacist is not a one-time event.

We have found that patients often research their disease state and therapies through various means such as the internet or discussions with other patients, family, and friends. This is encouraged to promote knowledge and support throughout their treatment. However, with the increasing trend of holistic and alternative health movements, patients may begin taking over-the-counter (OTC) supplements or herbal medications without discussing it with their providers. For example, I recently consulted with a myeloma patient who was taking 21 different supplements. Pharmacists must check for herbal and synthetic supplements—especially high-dose vitamins, which can affect the efficacy of chemotherapy treatment or exacerbate a patient’s disease. For example, if a newly diagnosed patient with hypercalcemia is taking excess calcium OTC, we need to address this issue. After discussing the situation with the team, we inform the patient of the appropriate calcium supplementation strategy. This may include discontinuation of the supplement, decreasing the dose, or replacing it with a simple multivitamin.

Our fundamental approach to the symptom of anemia in MM is to provide effective antimyeloma treatment, which should elevate and stabilize red blood cell counts. We do provide transfusions if necessary, when the hemoglobin is <10 g/dL, or hematocrit is <25%. Given the fact that many of our patients’ treatments include thalidomide or lenalidomide, we seldom use erythropoietins to treat chronic anemia. Both thalidomide and lenalidomide can put patients at an increased risk of developing a VTE. The addition of erythropoietins would further increase this risk; therefore, we do not use these agents concurrently. This is a cautious interpretation of guidance from the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO), which also warns against the use of an erythropoietin in combination with lenalidomide or thalidomide plus corticosteroids.

Myeloma-related bone disease tends to be very painful, as is peripheral neuropathy (PN) that may result from bortezomib or immunomodulators used in the treatment of MM. Since we increasingly use the RVD regimen (lenalidomide, bortezomib, and dexamethasone) in newly diagnosed patients (Figure), we monitor closely for PN. Working with pain assessments provided by the nursing staff, the pharmacist plays a key role in developing a rational plan for pharmacologic management of nociceptive and neuropathic pain in the myeloma patient.

We rely on opioid medication, typically oxycodone or morphine, for bone pain, which requires us to be very cautious about opioid adverse effects. One must distinguish between opioid tolerance, a natural physiological response to these drugs, and opioid addiction, which has psychological ramifications. In our practice, we avoid the use of both acetaminophen and nonsteroidal anti-inflammatory drugs since these agents may affect liver and/or kidney func-
tion, as well as mask fevers, which can deprive us of a warning sign for infection in our frequently neutropenic patients. To a large extent, opioid therapy is very helpful with neuropathic pain. However, additional agents such as gabapentin or pregabalin can be useful as well. Other therapies that may also be used are alpha lipoic acid, L-carnitine, folic acid, and B complex vitamins.

What strategies can be used for the prevention of infection in patients with MM?

Many newly diagnosed MM patients experience a disease-related increase in infection risk; extensive disease, poor renal function, and compromise to plasma cells can produce poor health status. Add to that the risks of therapy, such as viral reactivation and neutropenia, and the result is a significant potential for infection. At our center, we ensure that every individual receives basic preventive care. Patients receive vaccines, including seasonal flu vaccine and, if not up-to-date, pneumococcal vaccine. Bortezomib use can increase the risk of herpes zoster reactivation, therefore, if a patient receives this agent as part of the treatment regimen, we always include antiviral prophylaxis with acyclovir or another drug in its class. Pneumocystis carinii pneumonia (PCP) is always a concern in patients receiving high-dose steroids. If a steroid is part of the patient’s treatment regimen, we will begin prophylaxis for PCP. With regard to the use of prophylactic antibiotics and antifungals, we are selective and commensurate with recommendations from the National Comprehensive Cancer Network. We simply do not want to add the adverse events of antimicrobial agents if not necessary.

From my perspective, education is an extremely important aspect regarding infection control. When counseling patients for the first time, I typically ask if they have a history of herpes viral infections, cold sores, or zoster. If they report recurrent zoster infections, this would prompt me to consider the use of valacyclovir, if acyclovir has previously not been effective.

Bisphosphonates are a mainstay of therapy for myeloma-related bone disease, but their use can be complicated by certain CRAB symptoms. What is your approach to bisphosphonate use in patients with renal dysfunction or hypercalcemia?

The bisphosphonate we use the majority of the time is IV zoledronic acid, administered monthly for 2 years, then every 2 to 6 months, depending on the patient’s status at that time. An advantage of zoledronic acid is a relatively short IV infusion time of at least 15 minutes.17 Zoledronic acid also produced favorable outcomes in the recent Medical Research Council Myeloma IX study.18 However, this bisphosphonate must be dose-adjusted downward in increments, ranging from 4 mg to 3 mg, as patients’ baseline creatinine clearance falls from a normal value (>60 mL/min) to 30 mL/min; zoledronic acid is not recommended in patients with severe renal insufficiency (creatinine clearance <30 mL/min).12,17 Although the prescribing information for zoledronic acid suggests that the criterion for dose adjustment is the baseline creatinine clearance, we assess serum creatinine and calculate clearance at each visit and adjust the dose accordingly. We will also infuse zoledronic acid over 30 minutes rather than 15 minutes. For patients with significant renal impairment, we often elect to use pamidronate infused over 2 to 4 hours.1,17

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The approach is different, however, when hypercalcemia complicates the clinical picture. A newly diagnosed MM patient presenting with hypercalcemia will receive aggressive, acute treatment with zoledronic acid, which is the preferred bisphosphonate for this condition.19 Per our institutional guidelines, zoledronic acid dosing for hypercalcemia is 4 mg as a single-dose IV infusion over 30 minutes, followed by close monitoring to assess if further treatment is needed. No specific dose adjustment is suggested for patients with renal impairment. Similarly, if a patient with renal impairment is receiving zoledronic acid monthly, and we detect the emergence of hypercalcemia, we will administer a 1-time, full 4-mg dose, rather than adjusting the dose for renal dysfunction.

There are situations in which a switch from zoledronic acid to pamidronate may be necessary. We look for trends in serum creatinine and...
creatinine clearance with our patients, and if we notice a trend toward worsening renal insufficiency, with serum creatinine rising, we may discontinue the zoledronic acid and begin pamidronate, with the infusion rate at the slower end of the recommended time.\(^\text{17}\)

**How do you reduce the risk of disease- or treatment-related VTE in newly diagnosed patients?**

We ensure that all patients with thromboembolic risk factors, specifically those receiving thalidomide- or lenalidomide-containing regimens, receive VTE prophylaxis. Clinicians should be aware of the increased risk of VTE in the MM population—typically older patients with a disease that exacerbates thrombosis—regardless of therapy. Many patients present with a history of VTE, or with comorbidities that can increase the risk of thrombus formation. Numerous patients may already be taking warfarin or low-molecular-weight heparin, which we continue as their VTE prophylaxis.

**Conclusion**

It is vitally important for all members of the interdisciplinary cancer care team to understand the complexity of MM. Symptoms of the disease, including hypercalcemia, renal insufficiency, anemia, and bone disease, will influence not only which therapies can be used, but the dose and duration of treatment. Myeloma-related complications may change over time, as the disease responds to treatment or progresses. In addition, drug-drug interactions have the potential to cause clinical emergencies, which require immediate interventions. The pharmacist plays a key role in identifying these complex relationships, counseling patients, and monitoring responses to various therapies to ensure optimal clinical outcomes.\(^\text{18}\)

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**Evolving Concepts in the Management of Newly Diagnosed Multiple Myeloma**

*Continued from page 25*


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**References**


