It is estimated that this year alone, approximately 21,000 individuals in the United States will be diagnosed with multiple myeloma (MM), and more than 10,000 deaths will be attributed to the disease.1 Response rates and survival have improved considerably over the past several decades, due in large part to the use of high-dose chemotherapy, stem cell transplantation, and the development and approval of the targeted agents thalidomide, lenalidomide, and bortezomib.2 Although these advances have resulted in prolonged remissions and better quality of life, virtually all patients with MM relapse or become refractory to treatment and eventually, die from the disease.

Some patients with myeloma respond well to initial therapy but experience disease progression in the absence of treatment. These individuals are referred to as having relapsed MM. Others do not respond to initial therapy, and have what is known as primary refractory MM. There is also a subset of patients who have relapsed and refractory MM, defined by disease progression during a specific therapy or within 60 days of their last treatment.3 The safe and effective treatment of relapsed and/or refractory MM remains an area of intense focus for investigators and clinicians, and new agents for use in the late-line setting continue to be evaluated in clinical trials.

On January 20-21, 2012, nurses and pharmacists from around the country gathered in Houston, Texas to discuss current challenges and recent advances in the late-line setting for myeloma. The following articles provide perspectives on important issues that were discussed during this roundtable.

The management of disease- and treatment-related complications, both in clinical trials and in everyday practice, was considered a high priority by participants, and several discussions focused on strategies to help patients with relapsed and/or refractory myeloma remain on therapy. In addition, both nurses and pharmacists alike thought there was a need for more information related to the optimal use of investigational agents, including treatment-related adverse events, potential drug-drug interactions, administration guidelines, methods of reconstitution, and avenues for providing education to healthcare professionals and patients.

In light of the rapidly evolving therapeutic landscape for relapsed and refractory myeloma, and the special needs of this difficult-to-treat population, the sharing of knowledge, concerns, and insight among nursing and pharmacy professionals in the field remains essential for ensuring optimal patient care.

References
Managing Adverse Events in the Late-line Setting for Multiple Myeloma

Laura McBride, RN, BSN, OCN®, CCRP
Multiple Myeloma Division Oncology Research Nurse Coordinator
John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Introduction

With the implementation of novel targeted therapies and more effective supportive care measures, we are seeing improved outcomes in patients with multiple myeloma (MM).¹ The immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the first-in-class proteasome inhibitor bortezomib are commonly used to treat patients with MM, in both the front-line and relapsed and/or refractory settings.² Despite the proven efficacy of these agents,² nearly all patients eventually experience disease progression. Therapeutic options for these individuals are limited, and prognosis remains poor.³ In a recent study of patients with myeloma who relapsed or were refractory to bortezomib and IMiDs, median overall survival and event-free survival were 8 months and 5 months, respectively.⁴

Myelosuppression

Anemia, thrombocytopenia, and neutropenia are common and expected complications in patients with MM. They can be caused by the disease itself or may be a result of antimyeloma therapies, including lenalidomide, thalidomide, and bortezomib (Table).⁵ In addition to closely monitoring blood counts to assess the severity of myelosuppression, it is also necessary to consider factors such as patient comorbidities, institutional protocols, and current treatments when determining appropriate interventions. For example, grade 1 and 2 anemia may be treated with erythropoietin-stimulating agents (ESAs), but this practice varies from one center to the next. Nurses also need to be aware of the increased risk for thrombosis in patients who are being treated with IMiDs when ESAs are used at the same time, and must take the necessary precautions.⁶ Although effective treatment of the myeloma itself often results in a resolution of anemia, hemoglobin levels of 6.5 to <8.0 g/dL typically necessitate transfusion, as well as dose interruptions and/or modifications of agents such as lenalidomide or bortezomib.⁷ Similarly, dose reductions, temporary discontinuation of therapy, and in some cases, growth factor support, may be necessary for patients who develop neutropenia, depending on severity.⁸ In the case of thrombocytopenia, careful assessment of platelet counts helps to determine whether treatment should be held or dose attenuated, and when transfusion may be an appropriate course of action. It is important to note that although thrombocytopenia is a common toxicity associated with bortezomib, platelet levels typically decrease during each cycle of treatment, and return toward baseline between cycles.⁹

Peripheral Neuropathy

Many patients present with PN at the time of diagnosis. This complication is also a common AE associated with the use of agents such as thalidomide and bortezomib.⁸ Signs and symptoms of PN include temporary numbness, tingling, sensitivity to touch, and muscle weakness. However, this AE may also cause permanent paresthesias and more intense symptoms of pain, as well as muscle wasting and organ dysfunction, which can result in problems related to digestion, blood pressure, and bodily functions.⁸

It is important to obtain a baseline assessment of PN,
and then perform follow-up assessments regularly to determine grade and severity. Nurses must also educate their patients to report symptoms early so that the appropriate steps can be taken to address this toxicity.

Pharmacologic interventions to relieve pain involve a number of options, including the use of pregabalin, gabapentin, and norriptiline. It is often necessary to reduce the dose of specific antimielyoma therapies until symptoms improve; this is essential to prevent permanent neurologic damage. Bortezomib-associated PN tends to be reversible in most patients after dose modification or treatment discontinuation. Thalidomide-associated PN has a greater propensity to be irreversible, and may be related to higher cumulative doses and longer treatment duration.

The management of this toxicity in the late-line setting for MM remains a significant challenge, as there must be a careful balance between providing effective therapy for the disease and not aggravating preexisting symptoms.

Renal Dysfunction
Approximately 20% to 60% of patients with MM will experience renal insufficiency or kidney failure during the course of their disease. As with myelosuppression and PN, renal complications may be related to myeloma or specific therapies. It is important to ascertain the source of renal impairment to ensure proper supportive care. Close monitoring of creatinine clearance levels is essential, and patients must remain properly hydrated, but not to the point where they experience fluid overload. Treating the myeloma and reducing tumor burden often results in improved renal function. Some agents used in the treatment of relapsed and/or refractory MM, however, must be dose-adjusted for renal insufficiency; others cannot be administered when individuals are receiving dialysis. As a patient’s renal function fluctuates during the course of the disease, our management approaches continually need to be adjusted accordingly.

Conclusion and Future Directions
It is imperative for nurses to share with each other their knowledge and experience related to effective supportive care strategies and the management of AEs commonly seen in the late-line setting. There is also a need for novel drugs that can provide patients with safe and effective options when they relapse or become resistant to currently used therapies. An investigational agent that is showing promise for such patients is carfilzomib, a next-generation proteasome inhibitor. This agent has demonstrated clinical activity and good tolerability in patients with relapsed and/or refractory myeloma, including individuals who were heavily pretreated and those with specific comorbidities.

As new treatments continue to be developed and evaluated in clinical trials, we need to stay informed about the efficacy of these agents, as well as their toxicity profiles and the recommendations for minimizing AEs. There should be a diverse methodology for the dissemination of this information to ensure that healthcare professionals and patients are educated at levels appropriate to their needs. As nurses, we must remain vigilant in our efforts to effectively treat the disease, as well as care for the other needs of our patients, to ensure the best quality of life.

References

Table. Incidence of Grade 3/4 Hematologic Toxicities with Commonly Used Antimyeloma Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide*</td>
<td>21%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Thalidomide*</td>
<td>13%</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>Bortezomib*</td>
<td>15%</td>
<td>29%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Combined with dexamethasone in patients who had received ≥1 prior therapy.

*Combined with dexamethasone in newly diagnosed patients.

*In patients who had received 1 to 3 prior therapies.

Challenges in the Late-line Treatment of Multiple Myeloma
Challenges in the Treatment of Relapsed and/or Refractory Myeloma

Timothy Tyler, PharmD, FCSHP
Director of Pharmacy Services, Comprehensive Cancer Center
Desert Regional Medical Center, Palm Springs, CA

Introduction

Multiple myeloma (MM) is often diagnosed after a seemingly harmless activity, such as hopping off a curb, results in an unexpected bone fracture. Regardless of the method by which a patient discovers that he or she has myeloma, it is a very traumatic experience. Fortunately, the management of this debilitating disease has come a long way. Several decades ago, the cutting-edge regimen for MM was melphalan plus prednisone. However, this combination was associated with significant toxicities and some rather complex preparation issues related to the use of melphalan. Soon after, thalidomide, lenalidomide, and bortezomib began to arrive on the scene, and we saw improvements in patient outcomes. Unfortunately, we are still dealing with a disease that is associated with significant morbidity and mortality, especially in the late-line setting. As a result, the search continues for more effective supportive care strategies and new agents that can improve patient outcomes.

Strategies for Managing Adverse Events in the Late-line Setting for Multiple Myeloma

One of the adverse events we commonly see in patients who are treated with bortezomib and thalidomide is peripheral neuropathy (PN). With the exception of skeletal-related events, this complication probably takes the most time and energy when it comes to management strategies in the late-line setting, and dose modifications are often necessary during treatment. Recently, a new mode of administration for bortezomib was approved, and many patients now receive the drug as a subcutaneous injection, which has been shown to reduce the incidence of PN without sacrificing efficacy. This method is generally well tolerated, although injection-site reactions do take some time to return to normal. We are also seeing good results with the investigational agent carfilzomib, a next-generation proteasome inhibitor that is structurally and mechanistically distinct from bortezomib. In addition to impressive efficacy, very low rates of PN are associated with the use of this agent, which is a pleasant surprise with a proteasome inhibitor.

Approximately 50% of patients with MM experience elevated creatinine levels, caused by excess light chains spilling over into the kidneys. Renal impairment is associated with higher tumor burden, more aggressive disease, and increased mortality. It also affects drug selection and dosing strategies. Over-the-counter nonsteroidal anti-inflammatory drugs can impair kidney function; therefore, it is important to ascertain whether patients are using these medications, so that we can offer them safe alternatives. The intravenous bisphosphonates zoledronic acid and pamidronate must be dose-reduced in patients with varying degrees of renal impairment. Lenalidomide use in moderate and severe renal impairment requires dose adjustment, as this drug is renally excreted. Since bortezomib is hepatically metabolized, dose adjustments are not required in patients with renal dysfunction. Recent data on the use of carfilzomib in the late-line setting for MM also points to good tolerability in renally-impaired patients.

Conclusion

As pharmacists, we need to be aware of the latest developments in MM, not only for our own knowledge, but so that we can pass this information along to our fellow clinicians and to patients. Individuals with myeloma are well informed about their disease and become excited at the prospect of new agents on the horizon. They know that they have years of therapy ahead of them, and demand that quality of life be factored into the equation along with efficacy.

References