Introduction: Multiple Myeloma

Richard Cook, PharmD

ABSTRACT

BACKGROUND: Multiple myeloma (MM) is the most common type of primary bone tumor, affecting approximately 50,000 patients in the United States. Although it is currently not curable, recent advancements in treatment are bringing myeloma closer to becoming a chronic disease instead of a terminal illness.

OBJECTIVE: To better understand the prevalence of MM as well as provide an overview of the costs associated with treatment.

SUMMARY: The goals of treatment in MM include eradicating all evidence of disease, controlling disease to prevent damage to target organs, preserving normal function and quality of life, relieving pain, and managing myeloma that is in remission. To achieve these goals, treatment must be individually tailored for each patient based on the patient's age, overall health status, symptoms, and laboratory test results.

Advancements in the understanding of the pathogenesis of myeloma and the role of genetic mutations are leading to a new standard of treatment. Advancements in diagnostic technology, such as cytogenetic testing, are also being used to tailor treatment for each individual to work toward achieving better response rates, longer periods of remission, and improved quality of life.

Increased costs associated with the improved therapies being used to treat MM, and the comorbid conditions associated with the disease, present a challenge to managed care. Health plans and formulary decision makers need to better understand the complexity of therapy to best use resources. The economic burden to the patient must also be considered when developing treatment strategies.

CONCLUSION: Better understanding of the pathophysiology of MM, including the role of cytogenetics, is leading to the development and use of novel agents and treatment options. Head-to-head studies comparing treatments must be performed to best balance the costs associated with treatment and the benefits of improved survival rates and maintaining quality of life.

J Manag Care Pharm. 2008;14(7)(suppl S):S4-S6

Copyright© 2008, Academy of Managed Care Pharmacy. All rights reserved.

Author

RICHARD COOK, PharmD, is Manager, Clinical and Quality Programs, Pharmacy Services, Blue Care Network of Michigan, Grand Rapids, Michigan.

AUTHOR CORRESPONDENCE: Richard Cook, PharmD, Manager, Clinical and Quality Programs, Pharmacy Services, Blue Care Network of Michigan, Grand Rapids, MI 49516. Tel.: 616.285.3072; Fax: 616.956.5866; E-mail: rcook1@bcbsm.com

■ A Balancing Act

In the past 50 years, treatment for multiple myeloma (MM) has improved, with the most significant advancements within the past decade, leading to a paradigm shift in the treatment of MM. Although MM is still an incurable disease, studies show that introduction of novel therapies early in the course of MM may have an impact beyond that related to disease response, because they may improve the natural course of the disease.¹⁻³ Several major advancements in therapeutic options for MM were made between 1962 and 2005.¹ In the early 1960s, the introduction of melphalan in combination with prednisone in the treatment of MM led to improved survival. More intense chemotherapy regimens increased response rates, but with no improvement in survival, compared with melphalan and prednisone. In 1996, autologous stem cell transplantation was applied widely in the management of younger patients with myeloma after randomized trials demonstrated a survival advantage for this modality, compared with the conventional chemotherapy of the time. In the late 1990s, results of a study by Singhal et al. showed that thalidomide use in patients with MM demonstrated improved response rates and progression-free survival rates, compared with dexamethasone alone, and when thalidomide was added to the melphalan-prednisone regimen, improved survival was also noted.^{1,2}

Two major milestones in myeloma therapy have been realized since 2003. The first was the advent of bortezomib in May 2003. The first novel proteasome inhibitor of its kind in any therapeutic class, bortezomib was found to improve survival, compared with high-dose dexamethasone in patients with relapsed MM. Tandem autologous stem cell transplantation was found to improve survival, compared with single transplantation.^{1,4,5} On June 20, 2008, just before the publication of this supplement, the Food and Drug Administration approved bortezomib as frontline therapy in MM.⁶

The second milestone was the introduction of lenalidomide in 2005. In phase 3 trials, lenalidomide in combination with dexamethasone demonstrated improved survival, compared with dexamethasone alone, in relapsed MM. Additionally, improved supportive care, especially better access to growth factor support, decreased incidence of fractures and resultant complications due to widespread use of bisphosphonates, and better management of patients with renal failure have contributed to improving survival rates.^{1,7} These advances in overall survival and progression-free survival rates are truly exciting and have led researchers and clinicians to be highly optimistic that we are moving closer to making MM a chronic disease, if not a curable one. With the cost of stem cell transplants ranging from \$20,000 to \$60,000 and the annual cost of newer agents ranging from approximately \$27,000 to \$78,000 each,^{8,9} in addition to the costs of supportive care and diagnostic testing, the question arises: How can managed

care pharmacists provide high-quality care while still managing costs?

■ Background

MM, also known as myeloma or plasma cell myeloma, is the most common type of primary cancerous bone tumor. An estimated 50,000 patients in the United States have MM, with approximately 20,000 new cases being diagnosed each year. The average patient age at diagnosis is 68 years, and 99% of patients diagnosed are older than 40 years of age.^{10,11} Although MM is incurable, it is treatable. Treatment is complex and may include chemotherapy, radiation, and surgery.¹² Each treatment decision should be tailored to an individual patient's physical, emotional, financial, and medical needs. The goals of therapy include eradicating all evidence of disease, controlling the disease to prevent damage to target organs, preserving normal performance and quality of life, relieving pain associated with the disease, and managing the myeloma that is in remission.¹³

Optimal care includes access to cutting-edge medications, specialty and injectable therapies, and stem cell transplants.⁹ Therapy administration challenges are a major component of the financial burden of disease management. Formulary management strategies, in both evaluating treatment options and directing access to preferred oncology therapy, have evolved over the past 5 years. Cancer advancements and corresponding treatment guidelines will most likely continue to progress as new data are evaluated.

Genetic mutations play a large role in the pathogenesis of MM. Researchers have observed that karyotypic abnormalities have prognostic significance for patients with MM. Newer cytogenetic testing methods are now being used.

Patients with MM need constant monitoring and often suffer from other comorbid conditions that require additional tests and treatments. Managing comorbidities leads to better prognosis and quality of life for the patient with myeloma, yet it presents additional impact on the overall cost of managing the disease, as well as an increased burden on the patient.¹⁴

Although novel medications show great promise, accurate statements for the value of treatment are still needed. Clinical trials comparing various treatments head-to-head, instead of placebo-controlled studies, would need to be performed to help clarify efficacy statements. The need for such head-to-head studies is exemplified by the plethora of regimens recommended in the most recent National Comprehensive Cancer Network guidelines for MM.¹⁵ These studies must follow ethical standards of medical care and avoid the pitfalls of inferior comparators. A recent commentary in *Lancet* by Djulbegovic and Kumar pointed out the need to detect the real effects of new treatments, instead of continuing to use inferior treatments.¹⁶

Health plans and formulary decision makers need to better understand MM guidelines, treatment, and pharmacoeconomic considerations to begin the dialogue with their providers and find

a balance between providing health care that meets the standard of care and inappropriate use of their health care resources. The economic burden on the patient must also be taken into account. New drugs and improved treatments are transforming many cancers, including myeloma, into chronic diseases that are costly to manage, and insurers are scrambling to find ways to control expenses. Payers want the patient outcomes that physicians seek, although at a price that keeps the cost of health coverage manageable.¹⁷

The use of conventional agents, novel agents, combination therapies, and hematopoietic stem cell transplantation is responsible for markedly improved outcomes in MM. The median survival for patients enrolled in clinical trials has improved from 3 years during 1960-1990 to 5 years during 1990-2000. Researchers and clinicians expect that optimizing current regimens and using investigational agents will result in median survivals exceeding 7 years within the next 10 years. Also, as technologies that further define patients at risk for rapid disease progression are used and incorporated into routine practice, regimens specifically tailored to the genetic profile of each patient's particular myeloma may be used.¹⁸

This CME/CE activity offers recent information and provides strategies for approaching the burden, impact, and better management of this challenging disease. The pathogenesis and progression of MM as well as current treatment recommendations and emerging treatments will be covered.

DISCLOSURES

Dr. Cook provides consulting services related to the subject of this educational activity to Genentech, Inc., ICORE Healthcare, and Amgen, Inc.

REFERENCES:

1. Kumar SK, Rajkumar V, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-20.
2. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med*. 1999;341:1565-71.
3. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006;24:431-36.
4. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348:2609-17.
5. Attal M, Harousseau J, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495-502.
6. United States Food and Drug Administration. Bortezomib: supplemental new drug application approval letter (NDA 21-602/S-015). June 20, 2008. Available at www.fda.gov/cder/foi/applletter/2008/021602se1-015ltr.pdf. Accessed June 24, 2008.

7. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2007;25:LBA8025.
8. Cook R. An economic perspective on treatment options in multiple myeloma. *Managed Care Oncol*. Spring 2007;3:10-12.
9. Messori A, Trippoli S, Santarlasci B. Pharmacotherapy of multiple myeloma: an economic perspective. *Expert Opin Pharmacother*. 2003;4:515-24.
10. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer*. 2007;7:585-98.
11. Schwartzberg L. Managed care considerations in the treatment of multiple myeloma. *Managed Care Oncol*. Spring 2007;3:14-16, 47.
12. Merck Source. Multiple Myeloma: 2003. Available at: www.merck.com/mmhe/sec14/ch175/ch175c.html. Accessed March 9, 2008.
13. Multiple Myeloma Research Foundation. Intro to myeloma. Available at: www.multiplemyeloma.org/about_myeloma/index.php. Accessed March 9, 2008.
14. Barosi G, Boccadoro M, Cavo M, et al. Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. *Haematologica*. 2004;89:717-41.
15. The Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2008). National Comprehensive Cancer Network, Inc. Available at www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed April 27, 2008.
16. Djulbegovic B, Kumar A. Multiple myeloma: detecting the effects of new treatments. *Lancet*. 2008;371:1642-44.
17. Appleby C. Payers' costly battle against cancer. *Biotechnol Healthcare*. June 2005:18-25.
18. Katzel JA, Hari P, Vesole DH. Multiple myeloma: charging toward a bright future. *CA Cancer J Clin*. 2007;57:301-18.