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JOURNAL OF MANAGED CARE PHARMACY

Oncology Pharmacy Management and the Evolving Role of Managed Care: Recommendations for a Changing Environment with a Focus on Multiple Myeloma

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Supplement

October 2012

Vol. 18, No. 8-a

Continuing Education Activity

JMCP

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This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; 703.683.8416; 703.683.8417 (fax).

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Ms. Bugos is an active member of the Oncology Nursing Society and participates in her local Bay Area Chapter, where she serves on special interest groups including survivorship, nurse practitioner, nurse navigator, and BMT. In addition, she has served on the Patient Services Committee for the Leukemia and Lymphoma Society since 1999. Ms. Bugos is a clinical preceptor for UCSF nursing students. She participates in several local and national lecture series and conferences as a leading expert in long-term effects of therapy for hematologic malignancies.

Carol Ann Huff, MD, is Associate Professor of Oncology and Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland, and Director of the Multiple Myeloma Program in the Division of Hematologic Malignancies.

Dr. Huff's research interest focuses on the development of novel biologically-based therapies for multiple myeloma, including attempts to target myeloma stem cells and immune-based approaches. Her efforts focus on improving response rates and overall survival for patients with multiple myeloma, in part by seeking to target myeloma stem cells with new treatment strategies. She also works to reduce the toxicity of bone marrow transplantation and to develop targeted immune attacks post-transplantation.

Before receiving her medical degree from Baylor College of Medicine, Dr. Huff completed a bachelor of science degree in zoology at Duke University in Durham, North Carolina. She completed her internship and residency at the Johns Hopkins University School of Medicine and joined the Department of Medicine as an instructor and was later promoted to associate professor. Dr. Huff went on to complete a clinical fellowship in oncology and accepted a joint appointment in the Oncology Department.

Dr. Huff has authored many peer-reviewed articles, book chapters, and monographs in the field of myeloma research and is a leading national speaker on this topic.

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Dr. Mullins' research and teaching focus on pharmacoeconomics, comparative effectiveness research, and health disparities research. He has received funding as a principal investigator from the National Institute on Aging/National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute/NIH, and the Patient-Centered Outcomes Research Institute and was the Shared Resources Core Director for the NIH-sponsored University of Maryland Center for Health Disparities Research, Training, and Outreach. He also has served as a co-investigator on other grants funded by the Agency for Healthcare Research and Quality (AHRQ), Human Resources and Services Administration, and NIH. He served as a member of the Health Systems Research Study Section of the AHRQ and currently is a Regular Study Section member for the National Cancer Institute.

Dr. Mullins has designed many cost-effectiveness analyses and budget impact models through federal grants for both the pharmaceutical and insurance industries. He is co-editor-in-chief for *Value in Health* and is author/coauthor of more than 150 peer-reviewed articles and book chapters on pharmacoeconomics, outcomes research, and pharmaceutical policy and health disparities research in journals such as *The American Journal of Managed Care*, *The American Journal of Public Health*, *Cancer*, *Chest*, *Health Affairs*, *Health Services Research*, *Journal of Clinical Oncology*, *Pharmacoeconomics*, and *Social Science & Medicine*. Dr. Mullins was a member of the Maryland Health Care Commission Hospital and Ambulatory Surgical Facility Report Card Steering Committee. Before his graduate studies, he was an actuary and market researcher for the John Hancock Insurance Company. In 2002, he was the recipient of an Outstanding Service Award from the Drug Information Association, and in 2006 and 2008, he received an International Society for Pharmacoeconomics and Outcomes Research Service Award. In 2007, he received the Dr. Patricia Sokolove Outstanding Mentor Award from the University of Maryland, Baltimore, campus-wide Graduate Student Association.

The authors thank Keith Engelke, PhD, Impact Education, LLC, for writing assistance in preparation of this supplement. The authors would also like to thank Jack Aiello, multiple myeloma survivor and patient advocate, for his input on the topic in "Multiple Myeloma: Supportive Care Requirements and Coordination of Patient-Centered Care."

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A CME/CPE publication supplement based on a Continuing Professional Education Partner Program from the Academy of Managed Care Pharmacy 24th Annual Meeting & Expo held on April 18, 2012, in San Francisco, California.

Jointly sponsored by Impact Education, LLC, and Postgraduate Institute for Medicine. Postgraduate Institute for Medicine.

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This activity is designed to meet the educational needs of pharmacy directors, medical directors, clinical pharmacists, quality directors, care managers, and other managed care and payer organization professionals.

Learning Objectives

After completing this activity, the participant should be better able to:

1. Review indicators of treatment outcomes for multiple myeloma
2. Demonstrate the use of comparative effectiveness research as a decision support tool to appropriately invest resources and reduce treatment variability with multiple myeloma therapies
3. Recommend methods to improve patient outcomes with supportive care for multiple myeloma within a health plan setting
4. Evaluate innovative oncology pharmacy benefit models and specialty management services
5. Provide accurate and appropriate counsel as part of the managed care treatment team

Continuing Education Title

Oncology Pharmacy Management and the Evolving Role of Managed Care: Recommendations for a Changing Environment with a Focus on Multiple Myeloma

Release date: October 2012

Expiration date: October 31, 2013

Estimated time to complete activity: 1.5 hours

This activity is supported by an educational grant from Celgene Corporation.

Oncology Pharmacy Management and the Evolving Role of Managed Care: Recommendations for a Changing Environment with a Focus on Multiple Myeloma

STATEMENT OF NEED/PROGRAM OVERVIEW

The combination of better screening and diagnosis, novel therapies and innovative therapeutic regimens, and improved supportive care has increased survival rates for many patients with cancer. Treatment of multiple myeloma is a good example of this phenomenon. There are now several approved treatments for multiple myeloma, and although these agents improve clinical response and survival, they also increase drug costs. As a result, managed care organizations (MCOs) are increasingly focusing their resources on maintaining affordability while ensuring appropriate access and quality of care. In multiple myeloma, as in other malignancies, several factors influence the relative value of therapeutic interventions, including epidemiology and burden of disease, treatment variability, and availability of evidence-based practice guidelines. MCOs require robust economic and clinical data to make assessments of available treatment strategies; however, the evidence available to support informed decision making for the treatment of multiple myeloma is sparse and often of suboptimal quality. Utilizing the management of multiple myeloma as an example, this supplement recommends innovative approaches to oncology pharmacy management that find a balance between the need for cost control and enhanced clinical outcomes.

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MEDIA

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TYPE OF ACTIVITY

Application-Based

Introduction

Jeffrey D. Dunn, PharmD, MBA

ABSTRACT

BACKGROUND: The treatment of multiple myeloma continues to evolve as innovative therapies increase survival times and patient quality of life. The increasing availability and utilization of these novel therapies challenge health plan administrators to create a pharmacy benefit structure that minimizes barriers to patient access while simultaneously managing costs.

OBJECTIVES: To (a) enable decision making based on indicators of treatment outcomes for multiple myeloma (e.g., overall survival, progression-free survival, etc.) and markers of clinical efficacy (e.g., complete response, partial response, progressive disease, etc.); (b) coordinate oncology care and health plan medical and pharmacy management services to improve outcomes for patients with multiple myeloma; (c) enable the use of decision support tools to appropriately invest resources and reduce treatment variability with multiple myeloma therapies; (d) construct a benefit design model for multiple myeloma drugs; (e) recommend methods to improve patient outcomes with supportive care for multiple myeloma within a health plan setting; and (f) implement accurate and appropriate counsel, as part of the treatment team, that will improve patient adherence to treatment recommendations.

SUMMARY: The first article in this supplement, "Identifying Indicators of Outcomes and Implementing Treatment Pathways," reviews outcomes measures typically used in phase 3 clinical trials investigating novel oncology therapies and how these measures influence clinical decision making in the treatment of multiple myeloma. The second article, "Applying Oncology Formulary and Benefit Design Innovations to the Management of Multiple Myeloma in the Managed Care Setting," discusses how comparative effectiveness research is used to generate data that can be utilized by policy makers, plan administrators, payers, and patients to identify therapies that provide the greatest value. The third article, "Multiple Myeloma: Supportive Care Requirements and Coordination of Patient-Centered Care," identifies the elements of supportive care for multiple myeloma and discusses techniques to keep the patient experience as the focal point of the treatment plan.

CONCLUSION: Multiple myeloma is representative of a disease in which the introduction of novel therapies has increased survival and patient quality of life. Increasing use of these innovative yet expensive drugs has motivated efforts to redesign the oncology pharmacy benefit in a way that promotes both enhanced clinical outcomes and cost control. This process relies on robust economic and clinical data; however, these data are limited. To determine the best value-based strategies for the treatment of patients with multiple myeloma, managed care decision makers must continue to assess the evolving landscape of treatment options and consider both clinical outcomes and treatment costs in their analyses.

J Manag Care Pharm. 2012;18(8-a):S3-S29

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Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. More than 20,000 new cases are diagnosed annually in the United States, with an estimated 10,710 deaths resulting from the disease.¹ Although currently considered incurable, the treatment of multiple myeloma has improved dramatically over the past decade. The introduction of new treatment strategies (e.g., induction and maintenance), innovative new drugs (e.g., thalidomide, lenalidomide, bortezomib), new drug combination regimens (e.g., bortezomib/cyclophosphamide/dexamethasone, melphalan/prednisone/lenalidomide), novel interventions (e.g., autologous stem cell transplantation), and improved supportive care (e.g., bisphosphonates, pain management) has significantly expanded the therapeutic armamentarium.² It is estimated that survival now ranges from 1 year to more than 10 years, with a median survival of approximately 45 to 60 months.¹

With the availability of new agents and techniques, clinical decision making in multiple myeloma has become increasingly complex. Clinicians require data—ideally, data comparing survival outcomes of all treatment options with alternative interventions—to guide health care policy, benefit design, and therapeutic selection, but these data are rarely available. Consequently, comparative effectiveness research (CER) is frequently used to generate data that can be used to assess the value of competing therapies.

In an effort to improve the quality of patient care, health care decision making has become more evidence based and focused on outcomes. Ironically, in the headlong rush to improve the delivery of high-value care, there is a tendency to lose sight of the individual patient. Hence, several patient-centered research initiatives under way are designed to provide patients with the information they need to become fully informed consumers of health care products and services.³

Oncology pharmacotherapy and benefit design is rapidly evolving, providing both challenges and opportunities for managed care stakeholders. Payers must quickly assess the value of new treatments and work with plan administrators to modify the oncology benefit in a way that provides access to the novel intervention while simultaneously controlling costs. While new treatment options often promise improved disease control and possibly increased survival, patients and their physicians must work together to find the most appropriate fit of the new agent into the therapeutic regimen. Using multiple myeloma as an example, this supplement was designed to review the ongoing changes in oncology pharmacotherapy and provide insights on how to manage the impact of these changes. The first article, "Identifying Indicators of Outcomes and Implementing Treatment Pathways," provides a brief overview of how innovations in drug therapy have impacted the treatment of patients

with multiple myeloma. The authors highlight features of a successful multiple myeloma management strategy, including the use of evidence-based clinical pathways and treatment algorithms as well as the role of outcome measures such as overall survival to guide clinical decision making.

Evidence-based decision making is the hallmark of high-quality medical care. However, in many disease states, particularly cancer, robust evidence is often lacking. Hence, clinicians, policy makers, and patients are frequently required to make health care decisions without information on clinical outcomes or overall cost. In the second article, "Applying Oncology Formulary and Benefit Design Innovations to the Management of Multiple Myeloma in the Managed Care Setting," the authors provide an overview of CER and explain how this technique can be used to synthesize data to support therapeutic decision making, particularly as it relates to the creation of an oncology pharmacy benefit. Because the cardinal feature of CER is to help all people (including patients) make more informed decisions about health care, patient-centered outcomes research is also discussed.

Treatment of the active disease is only part of the therapeutic intervention because patients with multiple myeloma often require extensive supportive care to maintain an acceptable quality of life. In the third article, "Multiple Myeloma: Supportive Care Requirements and Coordination of Patient-Centered Care," the authors review the prophylactic and supportive treatments necessary to manage the bone disease, pain, venous thromboembolism, infections, anemia, hypercalcemia, renal dysfunction, and hyperviscosity frequently observed in patients with multiple myeloma.² Because the delivery of care in multiple myeloma is often fragmented and hindered by poor communication, lack of coordination, and minimal accountability,⁴ the authors introduce emerging patient-centered models of care designed to improve the delivery of multiple myeloma care.

Content for each article was drawn from the authors' presentations at the Continuing Professional Education Partner Program held in conjunction with the Academy of Managed Care Pharmacy's 24th Annual Meeting & Expo in San Francisco, California, on April 18, 2012.

Conclusion

Oncology pharmacy has been identified as a priority area for managed care for optimizing clinically and economically appropriate care for their members. With innovative treatments, many patients are living longer and thus require long-term therapy. With increasing duration of therapy, utilization and costs are increasing rapidly.⁵ To more effectively manage this utilization and costs, as well as to ensure continued delivery of high-quality care, managed care organizations must take the lead in making oncology pharmacy treatment and benefit decisions that will result in optimal patient outcomes.

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Identifying Indicators of Outcomes and Implementing Treatment Pathways

Carol Ann Huff, MD, and Jeffrey D. Dunn, PharmD, MBA

Well-designed clinical trials predefine a single indicator or “endpoint” as an objective measure to indicate whether the experimental treatment or intervention provides a clinical benefit.¹ Some endpoints may be surrogates or indicators that predict a real clinical outcome but do not necessarily have a guaranteed relationship with that outcome.¹ Use of different endpoints in clinical trials investigating treatments for the same disease or use of surrogate endpoints that do not accurately predict the clinical benefit confounds attempts to select among competing therapies^{2,3}—a challenge applicable to both prescribers and managed care decision makers responsible for selecting the most efficacious and cost-effective therapies and regimens for patients with multiple myeloma enrolled in the health plan.⁴ This article briefly reviews indicators of clinical benefit in multiple myeloma and describes how these indicators can be used to guide decision making when selecting drug therapies for inclusion in the multiple myeloma clinical pathway.

■ Assessing the Clinical Response in Multiple Myeloma

Historically, safe and effective treatments for patients with multiple myeloma have been limited; as a result, many promising drugs, such as melphalan, were rapidly incorporated into the treatment regimen with little understanding of the overall value of the therapy.⁵ However, recent approval of several new agents, including thalidomide, lenalidomide, and bortezomib, along with increased utilization of these therapies have led to efforts to quantify the value of multiple myeloma treatments and manage their use.⁶

Indicators of Clinical Efficacy: Multiple Myeloma Clinical Trials

Assessment of the value of a new therapy requires a standard against which to compare the novel agent. For the treatment of multiple myeloma and other cancers, the standard is prolonging survival or improving quality of life. If the effect of a new drug on survival or quality of life cannot be directly measured, a surrogate or indirect indicator of one or both of these treatment goals is often used.⁷ Currently, the U.S. Food and Drug Administration (FDA) considers overall survival (OS), defined as the time from randomization to an experimental arm in a clinical trial to death from any cause, to be the “gold standard” by which to evaluate new cancer therapies, including those for multiple myeloma.⁸ OS is precise, easy to measure, and free of bias; however, pursuing an OS endpoint in a clinical trial is time consuming and expensive and may not be required for accelerated regulatory approval.⁷

In 1992, the FDA began granting accelerated approval for

drugs that treat serious or life-threatening diseases that have not responded to other therapies.⁹ Accelerated approval has been sought for both newly developed agents (e.g., bortezomib) as well as for older drugs with potentially new indications (e.g., thalidomide). Accelerated approval is often granted based on the response of surrogate indicators of clinical benefit reasonably likely to predict OS or improvement in symptoms.⁹ Indicators or “surrogate endpoints” recommended by the FDA as valid predictors of longer survival, improved function, or symptomatic improvement are listed in Table 1. Drugs receiving accelerated approval must undergo further testing in larger, randomized clinical trials to confirm that the drug provides the clinical benefit predicted by the surrogate. If the additional trials do not confirm the clinical benefit predicted by the surrogate, the indication is rescinded, and the drug may be removed from the market.⁹ Between 1992 and 2010, 35 cancer drugs, including the multiple myeloma drugs thalidomide and bortezomib, received accelerated regulatory approval for 47 new indications.⁹ Clinical benefit was confirmed in 26 of the 47 (~55%) new indications after a mean interval of 4.7 years. Clinical benefit was not confirmed in 21 accelerated indications granted between 1992 and 2010.⁹

During the 1970s and well into the 1980s, the FDA approved cancer drugs based on the number of patients who responded to therapy (i.e., response rate) as determined by tumor assessments from radiological tests or physical examinations.^{8,10} Because response rates do not reliably predict improvements in survival, quality of life, physical functioning, or tumor-related symptoms, the FDA began to move away from reliance on the response rate and adopted the position that cancer drug approval should be based on more robust evidence that treatment was providing a clinical benefit.⁸ By the end of the 1990s, complete response, defined as the response of several biomarkers (e.g., number of plasma cells in the bone marrow, absence of the antibody M protein in the blood or urine) to treatment, had become increasingly common in multiple myeloma trials.^{10,11} However, few patients receiving chemotherapy regimens considered standard of care a decade ago (e.g., melphalan, vincristine, cyclophosphamide) exhibited a complete response.¹² In addition, concerns were raised about the ambiguity of the relationship between the biomarkers used to determine complete response and survival in patients with multiple myeloma.¹⁰

To address concerns with biomarker-based endpoints, a working group convened by the American Society of Hematology proposed using progression-free survival and time to progression as surrogates for OS,¹⁰ a position recently endorsed by the International Myeloma Working Group

Identifying Indicators of Outcomes and Implementing Treatment Pathways

TABLE 1 Endpoints Accepted by the FDA as Indicators of Clinical Effectiveness

Endpoint	Evidence		Advantage	Disadvantage
	Direct	Surrogate		
Overall survival: <i>Time from randomization until death from any cause</i>	√		<ul style="list-style-type: none"> Universally accepted Easily measured Precise 	<ul style="list-style-type: none"> Can be affected by therapies administered before and after experimental treatment Includes noncancer deaths
Symptom endpoints (patient-reported outcomes)	√		<ul style="list-style-type: none"> Provides patient perspective 	<ul style="list-style-type: none"> Data often missing Clinical significance of small changes is unknown Requires multiple analyses Lack of validated instruments to measure changes
Disease-free survival: <i>Time from randomization to recurrence of tumor or death from any cause</i>		√	<ul style="list-style-type: none"> Shorter follow-up and smaller sample size required vs. survival studies 	<ul style="list-style-type: none"> Definitions vary Not precisely measured Not statistically valid as a surrogate in all settings
Objective response rate: <i>Proportion of patients with tumor size reduction of a predefined amount and for a minimum time period</i>		√	<ul style="list-style-type: none"> Shorter follow-up and smaller sample size required vs. survival studies Effect attributable to the drug not natural history of the disease 	<ul style="list-style-type: none"> Not a direct measure of clinical benefit Not a comprehensive measure of drug activity Measures benefit only in the subset of patients who respond
Complete response: <i>Elimination of detectable disease</i>		√	<ul style="list-style-type: none"> Shorter follow-up and smaller sample size required vs. survival studies Durable complete response can indicate clinical benefit 	<ul style="list-style-type: none"> Not a direct measure of clinical benefit in all cases Not a comprehensive measure of drug activity Measures benefit only in the subset of patients who respond
Progression-free survival: <i>Time from randomization to objective tumor progression or death</i>		√	<ul style="list-style-type: none"> Can serve as primary trial endpoints Shorter follow-up and smaller sample size required vs. survival studies Includes measures of stable disease Generally based on objective/quantitative assessment 	<ul style="list-style-type: none"> Not valid in all settings Not precisely measured Subject to bias Definitions vary among studies
Time to progression: <i>Time from randomization to objective tumor progression</i>		√	<ul style="list-style-type: none"> Can serve as a primary trial endpoint Shorter follow-up and smaller sample size required vs. survival studies Includes measures of stable disease Generally based on objective/quantitative assessment 	<ul style="list-style-type: none"> Not valid in all settings Not precisely measured Subject to bias Definitions vary among studies

Adapted from: U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Clinical trial endpoints for the approval of cancer drugs and biologics. May 2007.⁸

FDA=U.S. Food and Drug Administration.

(IMWG) Consensus Panel 1.¹³ Progression-free survival is the time from start of the treatment to disease progression and is considered a surrogate marker for overall survival duration. It is also the recommended endpoint to use when describing multiple myeloma clinical trial results.² Time to progression is the time from start of treatment to disease progression, with deaths owing to causes other than progression of multiple myeloma not counted.² Compared with complete response, time to progression provides a more relevant assessment of treatment outcomes by providing a gauge of clinically meaningful progression in patients without the long follow-up and other concerns presented by directly measuring OS.¹⁴ Two novel multiple myeloma therapies recently received regulatory approval based on clinical benefit predicted by time to progres-

sion: lenalidomide and bortezomib. However, as suggested by the accelerated FDA approvals for 21 indications granted on the basis of surrogate data but unconfirmed with further testing, clinical benefit predicted by a surrogate may not always translate into an OS benefit.¹⁵

Indicators of Benefit: Clinical Practice

Assessing response to treatment is a key determinant of multiple myeloma management in the clinic.¹⁶ To more precisely assess response to treatment at the patient level as well as to facilitate comparisons between treatment strategies, the IMWG published uniform response criteria for multiple myeloma.² The IMWG criteria have been incorporated into the National Comprehensive Cancer Network (NCCN) clinical practice

TABLE 2 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Response Criteria	Definition
Complete response (CR)	<ul style="list-style-type: none"> Negative immunofixation on the serum and urine ≤ 5% plasma cells in bone marrow Disappearance of soft tissue plasmacytomas
Stringent complete response (sCR)	<ul style="list-style-type: none"> CR as defined above, <i>plus</i> normal free light chain ratio Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)	<ul style="list-style-type: none"> Serum and urine M protein detectable by immunofixation but not on electrophoresis, <i>or</i> ≥ 90% reduction in serum M protein level, <i>plus</i> Urine M protein level < 100 mg per 24 hours
Partial response (PR)	<ul style="list-style-type: none"> ≥ 50% reduction of serum M protein <i>and</i> ≥ 90% urine M protein reduction or to < 200 mg per 24 hours <i>and</i> ≥ 50% decrease in soft tissue plasmacytomas
Stable disease (SD)	<ul style="list-style-type: none"> Not meeting criteria for CR, VGPR, PR, or progressive disease (not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates)
Progressive disease (PD)	<ul style="list-style-type: none"> Increase of 25% from lowest response value in any of the following: <ul style="list-style-type: none"> Serum M component (absolute increase must be ≥ 0.5 g/dL), <i>and/or</i> Urine M component (absolute increase must be ≥ 200 mg per 24 hours), <i>and/or</i> Only in patients without measurable serum and urine M protein levels; the difference between involved and uninvolved free light chain levels (absolute increase must be > 10 mg/dL) Only in patients without measurable serum and urine M protein levels and without measurable disease by free light chain levels, bone marrow plasma cell PC percentage (absolute percentage must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium level > 11.5 mg/dL) that can be attributed solely to the plasma cells proliferative disorder
Clinical relapse	<ul style="list-style-type: none"> Clinical relapse requires one or more of the following: <ul style="list-style-type: none"> Direct indicators of increasing disease and/or end organ dysfunction (CRAB^a features); it is not used in calculation of time to or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions Definite increase in the size of existing plasmacytomas or bone lesions; a definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL) Decrease in hemoglobin of ≥ 2 g/dL Increase in serum creatinine by ≥ 2 mg/dL
Relapse from CR ^b	<ul style="list-style-type: none"> Any one or more of the following: <ul style="list-style-type: none"> Reappearance of serum or urine M protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Adapted from: Durie BG, Harousseau JL, Miguel JS, et al; International Myeloma Working Group. International uniform response criteria for multiple myeloma.²

^aCRAB features: hypercalcemia, renal insufficiency, anemia, and bone lesions.

^bAll relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

^cFor purposes of calculating time to progression and progression-free survival, patients with CR should also be evaluated using the criteria listed above for progressive disease.

cm = centimeter; dL = deciliter; g = gram; mg = milligram.

guidelines for multiple myeloma and include the following: complete response, stringent complete response, very good partial response, partial response, stable disease, progressive disease, clinical response, and relapse from clinical response (Table 2). Each response criterion is defined by specific biochemical changes occurring in response to treatment, which are described in detail elsewhere.^{2,13}

Therapeutic Decision Making in Multiple Myeloma

Multiple Myeloma Treatment Overview

Multiple myeloma typically follows a relapsing course, with the clinical benefit of treatment decreasing with each subsequent line of therapy.¹⁷ In the absence of definitive cure, the goal of treatment is to improve patients' long-term outcomes, including prolonging progression-free survival and OS.¹⁷ Therapeutic selection is influenced by the patient's overall

FIGURE 1 Treatment Pathway for a Patient with Newly Diagnosed Symptomatic Multiple Myeloma

Adapted from: Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management.²⁰

health, age, prior therapy, and the presence of symptoms, comorbidities, and/or disease complications.¹⁶ Up to 25% of patients present with asymptomatic disease and may remain stable for 10 to 15 years.¹⁸ In these patients, treatment is typically withheld until the patient develops active or symptomatic myeloma because early intervention has not been shown to affect survival.¹⁹

Treatment of symptomatic patients generally follows a 2-step approach: a relatively short period of initial (or induction) therapy followed by a longer maintenance phase (Figure 1).²⁰ The primary options for therapy include standard chemotherapy such as melphalan, cyclophosphamide, doxorubicin, and liposomal doxorubicin; corticosteroids such as dexamethasone and prednisone; newer drugs such as thalidomide, lenalidomide, and bortezomib; and stem cell transplantation.¹⁶ The NCCN recommends induction (i.e., initial) therapy with thalidomide, lenalidomide, or bortezomib plus autologous stem cell transplantation (ASCT) for younger patients (generally younger than 75 years of age) who present without comorbid heart, lung, renal, or liver disease (Table 3).¹⁶ Use of alkylating therapies such as platinum chemotherapies in the induction phase should be limited to avoid compromising stem cell reserve before stem cell harvest in transplant-eligible patients.²⁰ Various combinations of melphalan, dexamethasone, and prednisone with thalidomide, lenalidomide, or bortezomib are recommended for patients ineligible for trans-

plant due to significant systemic comorbidities or advanced age (generally older than 75 years).²¹ Once the best remission has been achieved, the induction phase should be followed by maintenance therapy with lenalidomide or thalidomide, with or without corticosteroids, which can prolong remission but not survival.¹⁶ A third phase of treatment, salvage therapy, may be initiated in patients who experience a relapse following a stem cell transplant or in patients with primary progressive disease following an initial transplant.¹⁶ Salvage therapy can also be used in patients who are ineligible for a stem cell transplant with progressive or relapsing disease after initial induction therapy. If a sustained remission was obtained with initial therapy, then consideration should be given to using it again.¹⁶ Salvage regimens recommended by the NCCN are listed in Table 3.

Clinical Indicators and Treatment Selection

One important factor widely associated with improved progression-free survival and OS in multiple myeloma is the quality of response to treatment and, in particular, the achievement of a durable complete response. Complete response represents elimination of detectable disease by currently available laboratory methods.¹¹ Many oncologists believe complete response is a good surrogate for survival and the key to long-term disease control because several studies suggest that complete response is correlated with survival.^{22,23} However, achievement of complete response is highly dependent on the treatment regimen; complete response was not common with conventional chemotherapy such as melphalan and prednisone or vincristine, doxorubicin, and dexamethasone.¹² Although these regimens demonstrated antimyeloma activity in more than half of patients, treatment was generally not sufficiently intensive to eliminate all traces of disease.²⁴ The value of complete response as a valid surrogate of clinical benefit did not become evident until the introduction of treatment regimens that used high-dose chemotherapy (HDT) in the initial or induction phase of treatment followed by ASCT.^{11,25} Compared with conventional chemotherapeutic regimens, HDT followed by stem cell transplant increased complete response rates to as high as 50%, and this was associated with longer progression-free survival and OS in most randomized studies.²⁶ High complete response rates have also been observed in patients treated with lenalidomide, thalidomide, and bortezomib compared with those receiving conventional chemotherapeutic regimens.²⁷ At this point in time, the evidence suggests that lenalidomide, thalidomide, and bortezomib are associated with improved OS from the time of diagnosis^{28,29} as well as delaying the time to relapse.³⁰

It is important to note that responses reported as complete response in the literature are not necessarily uniform and may therefore represent different levels of disease control based on the criteria used in the study.²⁴ For example, the duration of the complete response may be a stronger predictor of OS

TABLE 3 Multiple Myeloma Therapies

Primary therapy ^a for transplant candidates (assess for response after 2 cycles)	<ul style="list-style-type: none"> • Bortezomib/dexamethasone^b (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone^b • Bortezomib/lenalidomide/dexamethasone • Bortezomib/thalidomide/dexamethasone^b • Lenalidomide/dexamethasone^b 	<ul style="list-style-type: none"> • Dexamethasone^c • Liposomal doxorubicin/vincristine/dexamethasone (DVD)^c • Thalidomide/dexamethasone^c
Primary therapy for nontransplant candidates (assess for response after 2 cycles)	<ul style="list-style-type: none"> • Bortezomib/dexamethasone • Lenalidomide/low-dose dexamethasone^b • Melphalan/prednisone/bortezomib (MPB)^b • Melphalan/prednisone/lenalidomide (MPL)^b • Melphalan/prednisone/thalidomide (MPT)^b 	<ul style="list-style-type: none"> • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD)^c • Melphalan/prednisone (MP) • Thalidomide/dexamethasone^c • Vincristine/doxorubicin/dexamethasone (VAD)^c
Maintenance therapy	<ul style="list-style-type: none"> • Bortezomib • Lenalidomide • Thalidomide^b 	<ul style="list-style-type: none"> • Interferon^c • Corticosteroids^c • Thalidomide + prednisone^c
Salvage therapy	<ul style="list-style-type: none"> • Repeat primary induction therapy (if relapse at > 6 months) • Bendamustine • Bortezomib^b • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin^b • Cyclophosphamide/bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) and/or bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone^b • Thalidomide/dexamethasone 	

Adapted from: Anderson KC, Alsina M, Bensinger W, et al; National Comprehensive Cancer Network. Multiple myeloma.¹⁶

^aExposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve before stem cell harvest in patients who may be candidates for transplantation.

^bEvidence category 1 (high-level evidence, uniform National Comprehensive Cancer Network consensus that the intervention is appropriate).

^cEvidence category 2B (lower-level evidence, National Comprehensive Cancer Network consensus that the intervention is appropriate).

than simply achieving a complete response at some point in time.³¹ Additionally, although obtaining a durable complete response is associated with statistically significant longer OS in the majority of patients with multiple myeloma, there are some subgroups in which the relationship between complete response and OS is questionable, including rapidly-responding but early-relapsing patients, those with more indolent (i.e., slowly progressing) disease, and those with stable nonprogressive disease after induction therapy.¹⁸

The quality or depth of the complete response is another factor that appears to be associated with prolonged progression-free survival and OS.^{32,33} The depth of the complete response is defined by quantitative and qualitative changes in disease-related biomarkers as a result of treatment. Increasingly sensitive analytic techniques are now being explored to define more stringent degrees of complete response or elimination of minimal residual disease, including multiparameter flow cytometry and polymerase chain reaction.²⁴ Demonstrating eradication of minimal residual disease by these techniques has been shown to predict improved outcomes. High rates of complete response have been reported following consolidation therapy with novel agent-based regimens (i.e., a short course of treatment utilized to deepen the response achieved with induction

therapy).^{32,34} Use of these agents in the maintenance phase has also improved depth of response, delayed time to progression, and improved outcomes³⁵⁻³⁸ in younger and elderly patients.³⁹⁻⁴¹

Given the evidence arising from the clinical literature, complete response is now recognized as a surrogate for OS and as a clinically relevant endpoint in multiple myeloma studies.¹⁰ Complete response can also be considered an important therapeutic goal at all stages of treatment, and its routine measurement can be used to guide therapeutic interventions and assess response to therapy.¹⁰ It is important to note, however, that questions remain regarding complete response, and these questions may have implications on patient management. For example, it is not clear if all complete responses are equal in terms of depth of response and prognostic importance (i.e., whether complete response after HDT-ASCT is necessarily the equivalent of complete response achieved with nonintensive chemotherapy or with novel agent-based regimens). Answers to this and other questions await future investigation.²⁴

Clinical Pathways and the Management of Multiple Myeloma

Multiple myeloma represents a small percentage of all cancers treated in an oncology practice, but its associated clinical and

financial burden is disproportionately high.⁶ Of all cancers that affect the skeletal system, either as a primary tumor or due to metastatic disease, multiple myeloma had the highest mean cost per patient at \$132,615, compared with \$88,402 and \$65,287 for patients with breast or lung cancer, respectively, who developed metastatic bone disease.⁴² The growing cost of multiple myeloma care is being felt by all stakeholders, including payers, prescribers, and patients. Consequently, payers are increasingly focusing resources on managing costs while simultaneously providing patient access to treatment.⁴³ One key to controlling costs in oncology is to influence the prescribing process.⁴⁴ Although both private and governmental payers are developing and implementing processes to influence prescribing patterns, collaboration between payers and prescribers is critical for long-term success of the management program.^{44,45} Although individual management strategies vary among payers, one increasingly common approach is to work with oncology providers to establish clinical pathways or management plans for multiple myeloma and other cancers.⁴⁴ At the most fundamental level, clinical pathways represent an agreement by oncologists to treat a patient with multiple myeloma in a certain way. Clinical pathways are a tool to standardize care, decrease resource utilization, and improve clinical outcomes as measured by accepted criteria such as complete response.^{43,45} A clinical pathway may also provide a framework in which new therapies and treatment regimens can be evaluated and provide a mechanism to improve communication and create shared ownership of treatment outcomes.⁴⁴

Developing a Clinical Pathway

A clinical pathway is devised and implemented by a group of oncologists in collaboration with a health plan.⁴⁶ Oncologists are primarily responsible for reviewing the current clinical evidence and, based on clinical outcomes, safety, tolerability, and convenience of dosing and administration, determine the most appropriate treatment. The value of the selected therapeutic interventions (i.e., for multiple myeloma, pharmacologic intervention as well as stem cell transplant), defined as clinical outcomes divided by costs, is also considered. The pathway is adopted by the oncology practice and operationally implemented; compliance is documented; and retrospective data monitoring is conducted to assess pathway appropriateness and accountability.⁴⁶ The clinical pathway is reviewed at regular intervals to incorporate newly released data and account for any change in practice standards.⁴⁶ Payers also have a role: the payer provides an incentive that encourages the oncology providers to comply with the clinical pathway.⁴⁴ This incentive should not represent the potential to break even, but rather to gain. The decision to not participate or comply with the clinical pathway cannot place the provider at a disadvantage compared with a colleague who is reimbursed

based on a standard fee schedule. On the contrary, compliance with the clinical pathway should result in a gain above the nonparticipatory rate.⁴⁴

Clinical Pathways in Multiple Myeloma

Clinical pathways have become established for the most common solid tumors. The number of individual practices that are using clinical pathways in oncology is unknown but growing, and the scope of clinical pathways varies across the payer landscape.⁴⁷ For example, Via Oncology, a subsidiary of the University of Pittsburgh Medical Center, has pathways that cover 17 types of cancer and include prognostic testing, chemotherapy and biologic therapy, supportive care, and radiation therapy. In contrast, BlueCross BlueShield of Michigan has instituted 3 regimens for treating patients with adjuvant low-risk breast cancer.⁴⁷ Among payers who adopted clinical pathway programs, breast cancer (83%) was the most common of the oncology subtypes, followed by lung (70%), colon/rectal (60%), multiple myeloma (43%), prostate (40%), kidney (38%), ovarian (38%), chronic lymphocytic leukemia (35%), liver (33%), and melanoma (30%).⁴⁸ CareFirst BlueCross BlueShield, which serves the Mid-Atlantic region, was one of the first payers to implement a clinical pathway for multiple myeloma.⁴⁴ Since its introduction in 2010, physician compliance with the pathway has increased to approximately 90%. Although additional data on the impact of the pathway on clinical outcomes and cost savings are not available at the current time, use of a similar pathway to guide treatment of breast, lung, and colon cancers resulted in a 10% reduction in the number of regimens utilized to treat these diseases as well as a gross savings to the health plan of 13% to 14% when financial trends in the participating group of patients were compared with those in the nonparticipating group.⁴⁴

Clinical Pathways and Treatment Guidelines

As therapeutic options for patients with multiple myeloma have increased, uncertainty has arisen about the optimal approach to therapy.¹⁸ Clinical practice guidelines published and regularly updated by the NCCN can guide therapeutic decision making for patients with multiple myeloma. These guidelines are considered the “gold standard” because they stratify treatment recommendations based on the strength of the clinical evidence and expert consensus where objective data are lacking. These guidelines describe the universe of treatment options in multiple myeloma and form a foundation for therapeutic decision making embraced by both oncologists and payers. However, multiple drugs and regimens receive the same recommendation, and thus, the guidelines provide little guidance on which treatment options offer the best combination of safety, tolerability, and clinical benefit.¹⁶ Clinical pathways bridge the gap between broad treatment recommendations provided by the

NCCN guidelines and the specific actionable steps for oncologists to consult and from which to create an individualized patient management plan. Well-designed clinical pathways incorporated into an electronic medical record system can also allow providers to review multiple peer-recommended options based on diagnosis, stage, and progression accompanied by the associated literature citations.⁴⁹ Furthermore, pathways based on evidence-based treatment guidelines can provide consistency in treatment and predictability, both of which are of significant interest to payers.⁴⁹

Summary

Well-designed clinical trials predefine a single indicator or endpoint as an objective measure to indicate whether the experimental intervention provides a clinical benefit. OS is considered the gold standard endpoint, but it is not always measured. When OS is unavailable, surrogate endpoints are relied on to predict the ultimate clinical outcome. Common surrogates for OS include progression-free survival and time to progression. With the advent of more effective therapies, complete response, a surrogate that had its usefulness questioned because of ambiguity in the relationship between the biomarkers used to assess complete response and clinical benefit, has re-emerged and is now widely used both as a clinical and an investigative tool to assess the depth and duration of a clinical response. Evidence gained from the use of these clinical indicators has been incorporated into clinical practice guidelines such as those published by the NCCN. Treatment recommendations contained within the guidelines form the foundation of clinical pathways used by many providers and payers to guide the treatment of patients with cancer. Although data are not yet available to determine this with any certainty, it is believed that use of clinical pathways in the treatment of patients with multiple myeloma will standardize care, decrease resource utilization, and improve clinical outcomes.

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Applying Oncology Formulary and Benefit Design Innovations to the Management of Multiple Myeloma in the Managed Care Setting

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There has been a marked increase in the number of treatments for multiple myeloma over the past 10 years. New drugs such as thalidomide, lenalidomide, and bortezomib have been shown to be active in multiple myeloma and are often combined with older agents such as melphalan to create potent treatment regimens (Table 1).¹ Although the development of these drugs provides patients with several new therapeutic alternatives, clinicians are now challenged to choose between several competing interventions when devising the safest and most effective management strategy for each patient. Health care policy makers, health plan administrators, payers, and patients are also challenged to select the therapy that provides the greatest value for their investment. Issues such as “off-label” use of drug therapies and data gaps, as well as potential solutions, such as comparative effectiveness research (CER), patient-centered health care delivery, and oncology drug benefit design, are discussed.

Off-Label Drug Use in Oncology

Decisions regarding patient management should be evidence based, yet more than half of the treatments received by patients are administered without clear evidence of clinical efficacy.² This is a particular challenge in oncology, an area in which many drug therapies are used outside their labeled indications. A survey of 3,500 office-based oncology practices identified at least 87 distinct oral anticancer therapies used off-label.³ Similarly, the National Comprehensive Cancer Network (NCCN) estimates that as many as 75% of all cancer drugs are used outside the scope of their specific approval.⁴ In multiple myeloma, oncologists frequently prescribe lenalidomide as first-line therapy. Although there are studies supporting the use of lenalidomide as a first-line therapy, it is only approved by the U.S Food and Drug Administration (FDA) for use in combination with dexamethasone for patients with multiple myeloma who have had at least one prior treatment.⁵

Several reasons have been put forward to explain why off-label use is so widespread in oncology. Oncologists frequently discover through clinical practice that different types of cancer share a common biology and thus sensitivity to a particular therapy. In such cases, off-label use can become widespread and possibly the standard of care without the support of a labeled indication.⁶ For some drugs, clinical trial data to support the use of the product outside the labeled indication are never generated, possibly because of the expense of pursuing a label expansion; in particular, once a drug nears the end of its patent life, manufacturers have little incentive to invest addi-

tional resources in the product.⁷ There is also the possibility that the product is never tested in novel disease types because of concerns that it may be inferior or equivocal to current care.⁸

Data Gaps

Regardless of why therapies are used off-label, a common denominator for many drugs used to treat multiple myeloma is the lack of clinical trial data that directly compare one treatment with another.⁹ The scarcity of comparative data not only makes it difficult for providers and patients to select the most appropriate therapy but also for plan administrators and payers to fully evaluate products for possible inclusion or preference in the health plan benefit. In addition, the paucity of evidence hinders public health policy makers in their efforts to assess the overall value of oncology therapies. A systematic review of the 4 compendia approved to provide the Centers for Medicare & Medicaid Services with guidance on oncology treatments, including multiple myeloma, noted that each compendium lacked current evidence and transparency on how the therapies included in the document were selected.⁸

Trial Endpoints

As discussed by Huff and Dunn in “Identifying Indicators of Outcomes and Implementing Treatment Pathways” (p. S5), overall survival (OS) is considered the most reliable cancer endpoint because, among other qualities, it is both precise and easy to measure.¹⁰ However, the cost and time required to measure OS has led to the use of endpoints that act as surrogates or indicators of expected clinical efficacy.¹¹ For some tumor types, response of the surrogate marker is predictive of an OS benefit—an outcome subsequently confirmed on further investigation—but this is not always the case.¹² In multiple myeloma trials, complete response is often the targeted endpoint; however, trial data may not be sufficiently robust to definitively indicate that the directional change in complete response is predictive of prolonged OS.¹³ This lack of confidence in trial endpoints creates challenges when designing the pharmacy benefit and for therapeutic decision making.

Patient-reported outcome (PRO) measures provide validated evidence of response to therapy from the patient’s point of view and may reflect underlying health status more accurately than clinician reporting.¹⁴ PROs are increasingly recognized as important for treatment and/or disease-related consequences that are directly experienced by patients, such as symptoms and health-related quality of life. Most phase 3 multiple myeloma trials fail to include well-designed

TABLE 1 Agents Approved for the Treatment of Multiple Myeloma

Drug	Trade Name	FDA Approval Date	Indication
Melphalan ⁵⁴	Alkeran	1962	Palliative treatment of patients with multiple myeloma
Bortezomib ⁵⁵	Velcade	May 2003	Patients with relapsed multiple myeloma
Thalidomide ⁵⁶	Thalomid	May 2006	In combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma
Lenalidomide ⁵	Revlimid	June 2006	In combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least 1 prior therapy
Pegylated liposomal doxorubicin ⁵⁷	Doxil	May 2007	In combination with bortezomib in patients who have not previously received bortezomib and have received at least 1 prior therapy
Bortezomib ⁵⁵	Velcade	June 2008	Patients with newly diagnosed multiple myeloma

FDA=U.S. Food and Drug Administration.

quality-of-life studies that can shed light on how patients in different risk categories benefit from various interventions.¹³ This may be changing, however, because several major regulatory and advisory entities, including the FDA¹⁴ and Patient-Centered Outcomes Research Institute (PCORI),¹⁵ are emphasizing the importance of incorporating PROs into cancer research and health care policy.

Comparison of Treatment Alternatives

Ideally, robustly designed randomized controlled clinical trials (RCTs) would simultaneously compare all interventions of interest. Unfortunately, such studies are almost never available because new drugs are often compared with placebo or standard care but seldom with each other because manufacturers have little incentive to conduct exhaustive comparative trials—their goal is to achieve regulatory approval as quickly as possible.^{16–18} Additionally, RCTs are seldom designed to answer pragmatic questions about the use of a new therapy in the context of existing treatment options or in patients who do not meet the inclusion criteria of the RCT.

Despite the lack of head-to-head trials, it is still necessary to compare the effectiveness of competing treatment alternatives to answer relevant policy questions.¹⁸ With relevant RCT-based comparisons lacking, indirect comparisons generated by decision analytic modeling tools are increasingly used to guide decision making. An indirect treatment comparison assesses the relative value of treatments that have never been directly

TABLE 2 Data Sources Used to Conduct Comparative Effectiveness Research

Primary Comparative Effectiveness Research

- Systematic reviews of existing research, including meta-analysis
- Decision modeling, with or without cost information

Secondary Comparative Effectiveness Research

- Retrospective analysis of existing clinical or administrative data, including “natural experiments”
- Prospective observational studies, including registries, that observe patterns of care and treatment outcomes; patients in these studies are not assigned to specific groups
- Experimental studies, including randomized clinical trials, in which patients or groups of patients are assigned to alternative treatments, practices, or policies

Adapted from: Tunis SR, Benner J, McClellan M. Comparative effectiveness research: policy context, methods development and research infrastructure.²²

compared but have been compared with a common comparator. For example, if regimen A has been compared with B, and B has been compared with C in randomized trials, indirect comparisons can provide insights on the relative effectiveness of A versus C.¹⁷ More complex modeling allows comparison of 4 or more interventions that have never been compared directly, providing decision makers with a powerful tool to evaluate competing treatment alternatives. Despite this utility, indirect comparisons make important assumptions about the stability of relative treatment effects across trials that are easily violated. Thus, in the absence of (head-to-head) RCTs, decision makers can use indirectly generated evidence as long as they are aware of the potential risks in using evidence of lower quality and that the potential benefits outweigh these risks.¹⁹

Comparative Effectiveness Research

CER involves assessment of a medical intervention against alternative interventions with the goal of identifying treatment approaches that are most likely to have preferable benefit-risk profiles or are considered cost-effective in real-world clinical settings.² CER results are intended to be relevant to a broad array of individuals who represent the wide variety of patients in the real world.²⁰ They can also be used to assist providers, payers, and patients in making informed health care decisions. Conducted in the United States since the 1970s, CER efforts recently received a significant boost in funding with the American Recovery and Reinvestment Act of 2009, with the additional funding earmarked for expansion of the infrastructure (e.g., databases, electronic health records, patient registries) and research (e.g., development of methodological best practices) necessary to assess the relative strengths and weaknesses of medical interventions.^{21,22} CER has been the basis for health care decision making for several years in several other countries, most notably the United Kingdom.²³

CER and Data Analysis

CER uses data from numerous sources (Table 2) to analyze the relative value of different interventions.²² “Primary” CER relies on systematic reviews of existing research, including meta-analysis, and decision modeling to establish a conclusion, whereas “secondary” CER uses retrospective analysis of clinical databases, prospective observational studies, and experimental studies, including randomized trials.²²

CER-based health care decision making requires comparisons of all relevant competing interventions. In reality, such studies rarely exist, so CER frequently relies on indirect treatment comparisons and network meta-analysis to provide useful evidence to guide selection of the best choice of treatment.¹⁹ The treatment with the greatest relative effect versus the common comparator is considered to be superior.²⁴⁻²⁶ CER also generates data using network meta-analyses. In contrast to a traditional meta-analysis, which includes only studies that compare the same intervention with the same comparator, a network meta-analysis includes multiple pairwise comparisons across a range of interventions.²⁷ Thus, a network meta-analysis provides estimates of the relative treatment effect on multiple treatment comparisons for comparative effectiveness purposes.²⁷ Mixed-treatment comparisons, a special case of network meta-analysis, combine direct and indirect evidence for particular pairwise comparisons, thereby synthesizing a greater share of the available evidence than a traditional meta-analysis.¹⁹

Both direct and indirect evidence contribute to the total body of evidence.¹⁶ Even when the results of the direct evidence are conclusive, combining them with the results of indirect estimates may yield a more precise estimate of the interventions directly compared and broaden inference to the population sampled because it links and maximizes existing information within the entire scope of treatment comparisons.²⁵

Application to the Prescribing Community

Use of the rigorous statistical analysis inherent to CER is accompanied by the risk that translation of the findings to the prescribing community, payers, and patients is lost in the complexity of the methodology used to generate the results.²⁸ In the real world, a trade-off occurs between the complexity of the methodology used to generate robust comparisons and ensuring the data generated are applicable and understandable to those stakeholders who require information to make decisions about benefit design, clinical pathways, formularies, and treatment decisions. Having patients, providers, health plan managers, and other decision makers participate in the design of comparative effectiveness studies can ensure that this research focuses on the evidence gaps most relevant to the parties who will be most impacted by its results.²⁸

TABLE 3 Features of Patient-Centered Outcomes Research

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people
- Is inclusive of an individual's preferences, autonomy, and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination
- Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, availability of services, technology, and personnel and other stakeholder perspectives

Adapted from: Patient-Centered Outcomes Research Institute. Patient-centered outcomes research.²⁹

■ Patient-Centered Health Care Delivery

Patients as Key Stakeholders in Health Care

The role of the patient in the health care decision-making process has recently risen to prominence.^{29,30} Patients are increasingly regarded as one of the key stakeholder groups that, alongside regulators, payers, and clinicians, influence access to and reimbursement for drug therapies. Recognition of the importance of the patient perspective is reflected by the creation of the Patient-Centered Outcomes Research Institute (PCORI) under the U.S. Patient Protection and Affordable Care Act.²⁹ PCORI was created to conduct research to provide information about the best available evidence to help patients and their providers make more informed decisions. PCORI is charged with conducting outcomes research designed to answer specific patient-focused questions about the benefits and harms of preventive, diagnostic, therapeutic, or delivery system interventions. PCORI addresses one of the primary concerns regarding health care in the United States: In many cases, patients and their families, caregivers, and even their health care providers do not have the information they need to make choices aligned with their desired health outcomes.³⁰ Outcomes of interest to PCORI include survival, function, symptoms, and health-related quality of life³⁰ (Table 3).

When patients have information, it allows them to have informed conversations with their medical oncologists and other providers about treatment strategies and therapeutic selection. If the patient has access to evidence indicating a particular therapy is beneficial, both the patient and provider may be more confident that spending limited health care resources on the therapy is a wise investment. The pharmaceutical industry also has an interest in patient-centered research because it is not to their advantage when the wrong patient receives the wrong therapy and experiences toxicities and adverse events.

Payers also benefit when the data used for benefit design include the perspective of the patient, particularly because patients are often asked to shoulder a significant burden of the drug cost through copayments and other cost-sharing structures.³¹

Applying a Patient-Centered Approach to Multiple Myeloma

Patient-centered data on multiple myeloma treatment are currently lacking. Some of the challenges stem from a lack of health literacy on the part of the patient.³² Others result from provider-related limitations such as a lack of time to explain complex information and a lack of tools to facilitate treatment planning, as well as insensitivity to patients' informational, cultural, and emotional needs.³² These challenges are compounded by difficulties in generating evidence utilizing CER techniques. Despite a growing number of treatments, there is limited evidence from new trials that allow generation of indirect treatment comparisons. In essence, there is a need for more real-world evidence outside of phase 3 clinical trials to inform value decisions.

For patient-centered research to be truly valuable, patients need to know how the evidence applies to them individually in terms of survival, toxicities, and cost.^{29,30} For example, knowledge that a drug increases progression-free survival and disease-free survival is helpful for regulatory approval, but what does this mean in terms of the likelihood of an individual patient surviving for another 3 or 5 years? How does the drug toxicity profile reported in the trial apply to a patient who may fall outside the inclusion criteria used in the study? Ultimately, data are needed so a patient can get answers to questions such as, "Given my characteristics as a patient with multiple myeloma and given my personal preferences in terms of trade-off for toxicities and extension of life, what therapy will provide me the best value for my money?" To answer these and similar questions, PCORI will conduct outcomes research assessing the benefits and harms of preventive, diagnostic, therapeutic, or health care delivery system interventions, highlighting comparisons and outcomes relevant to patients and their caregivers.³⁰

■ Cancer Drugs and Pharmacy Benefit Design

Spending on cancer drugs has risen faster than spending in many other areas of health care. Currently, sales of anticancer drugs are second only to those of drugs for heart disease, and 70% of these sales come from products introduced in the past 10 years.³³ In 2010, cancer treatments made up approximately 15% of total specialty pharmacy spending.³⁴ Most new therapies cost at least \$5,000 per month,³⁵ and cost-effectiveness ratios of many of these products can exceed commonly accepted thresholds, typically between \$140,000 and \$200,000 per quality-adjusted life year.³⁶

Although cancer drugs have been traditionally viewed as

"off limits" for utilization management strategies, the steady upward rise in cancer drug spending has triggered a vigorous debate about the overall value of oncology treatments in terms of clinical, pharmacoeconomic, humanistic, and societal endpoints.^{33,36} Payers are now motivated to apply payment reforms and quality measurements to cancer and approach the category like other chronic disease states.³⁷ However, a lack of good empirical evidence hinders attempts to manage oncology products.³⁸ Consequently, there is no standard to the oncology benefit design in the marketplace and most plans place specialty oncology drugs into the existing benefit and attempt to manage them using traditional utilization limits and cost controls.

Design Considerations

Although a standard oncology drug benefit has yet to emerge, several concepts are being implemented as plan administrators attempt to determine the overall value of treatments. Clinical practice guidelines from the NCCN and the American Society of Clinical Oncology serve as standards of medical care and as compendia for reimbursement for approved and for off-label uses of cancer drugs.⁴ There have been recent efforts to minimize variation in care through defining limited treatment pathways. Several managed care organizations now offer pathway programs that identify "preferred" options: either a single-treatment option per condition or a subset of treatment options per condition. These programs are often developed in a specific health plan market in collaboration with participating oncologists. Oncologists who achieve a specified level of pathway compliance may receive additional compensation.³⁹ Use of preferred pathways can also help drive utilization of specific drug products and therefore possibly maximize manufacturer rebates, further lowering net costs to payers. Plan members can be encouraged to utilize drugs identified with the preferred pathway, with lower out-of-pocket costs for preferred or generic agents.⁴⁰

In the past, traditional cancer treatment (i.e., chemotherapy) was primarily delivered intravenously or by injection, but orally administered drugs have become the standard of care for many types of cancer. Current pharmacotherapy for multiple myeloma includes 4 targeted therapies: 2 self-injectable agents and 2 orally administered drugs (the 2 orally administered therapies do not have intravenous or injectable equivalents).¹ Oral cancer drugs, including those for multiple myeloma, have historically been covered under the pharmacy benefit, which often means higher coinsurance or cost-sharing burden for patients, whereas injectable agents have been covered by the medical benefit, with fewer out-of-pocket costs.⁴¹ This convention is now changing, with many managed care organizations moving cancer drugs to the pharmacy benefit rather than the medical benefit; this is where high-cost drugs for multiple myeloma and other cancers are sometimes placed in a "higher tier," so that instead of having a specified copayment,

the patient is responsible for paying up to 50% coinsurance. Although the intent is to reduce the payer's financial risk, this approach makes these drugs unaffordable for many patients.³⁹

Cancer drugs have historically been insensitive to cost sharing,⁴² but as new and more expensive therapies become available, patients are facing a steady escalation of out-of-pocket costs for cancer treatments—in some cases exceeding \$35,000 per year.⁴³ In other therapeutic areas, high out-of-pocket expenses negatively affect patient adherence,⁴⁴ but currently there is little evidence in oncology to suggest that increased cost sharing results in poor outcomes. However, with efforts to increase patient awareness of the value of oncology therapies under way, it is feasible that patients may balk at paying a premium for cancer therapeutics that achieve only marginal benefits.

Data are crucial to the successful management of the oncology drug benefit because timely access to reliable data allows administrators to assess plan performance and adjust the benefit as trends arise.⁴⁵ In many practice settings, the electronic medical record system allows for the collection of pharmacy data originating at the point of care.⁴⁶ However, reliable data are not always available in some cases, especially under the medical benefit, where the timing of adjudication is often not synchronized with the pharmacy plan and consequently not reported as part of the National Council for Prescription Drug Programs performance report.⁴⁶ Lack of an integrated medical and pharmacy drug benefit may hinder the ability of pharmacy managers to capture and process claims originating in the medical benefit. Data on the total cost of care, including total cost, indirect cost, medical offsets, and cost of adverse effects, may also be lacking and therefore limit the ability to consider these inputs when making benefit design decisions. Further, cancer drugs covered in the medical benefit are often not tiered, resulting in similar copayments or cost-sharing amounts for all products and making it more difficult to provide incentives to physicians and patients for use of preferred products.

Value-Based Benefit Design

A value-based benefit design uses plan-based incentives to encourage patients to appropriately use recommended treatment pathways and engage in healthy behaviors to improve health outcomes and control or reduce costs.⁴⁷ A plan-based incentive may include reduction or elimination of patient cost sharing for services that show strong evidence of clinical benefit. Alternatively, patients may incur increased cost sharing if services that do not show evidence of clinical benefit are used. The most commonly implemented value-based benefit programs lower copayments on classes of medications identified as high value. For example, the program run by Pitney Bowes provides asthma and diabetes medications to its employees for free, and the company reported a 19% decrease in costs per asthmatic patient.⁴⁸ Value-based benefit designs are intended to focus on the long term. This approach may initially increase

the cost of care in pursuit of quality enhancements and hence should not be considered a strict cost-saving strategy. Rather, value-based benefit design is a means to increase value for the health care dollar.⁴⁹

Although a value-based benefit has been implemented by several payers and employer groups to manage chronic conditions such as diabetes^{48,50} and hypercholesterolemia,⁵¹ it is currently unclear if use of such a benefit results in improved health outcomes and controls or reduces health care costs. There may be a good fit for value-based design in the specialty oncology category due to the high cost of therapies used to treat a disease, with significant downstream costs and lower numbers of patients with the disease. If value-based design is integrated with other value-producing initiatives, such as CER, there is potential to lower costs for patients and health plans as well as improve treatment outcomes.

Accountable Care Organizations

The U.S. health care system remains fragmented; no single group of participants—physicians, hospitals, public or private payers, or employers—takes full responsibility for guiding the health of a patient or community; care is distributed across many sites; and integration among them may be deficient.⁵² Accountable care organizations (ACOs) were conceived as part of the health care reform legislation of 2009.⁵³ Under the new legislation, an ACO will assume full responsibility for meeting a proposed 65 quality measures involving prevention, diagnosis, treatment, continuing management, and aftercare of chronic diseases in a population of Medicare beneficiaries for at least 3 years.⁵³ As the legislation is currently written, oncologists and other specialists cannot start or manage an ACO, but they can join as many ACOs as they wish. In addition, of the quality measures outlined in the ACO law, only the preventive measures of screening for colon cancer and mammography relate specifically to cancer care.⁵³

The main purpose of an ACO is to foster change in patient care so as to accelerate progress toward better care for individuals, better health for populations, and slower growth in costs through improvements in care. If an ACO succeeds in both delivering high-quality care and reducing the cost of that care to a level below what would otherwise have been expected, it will share in the Medicare savings it achieves.⁵³ Accountable care should not be viewed as a panacea but rather one of a number of complementary initiatives chartered by the Affordable Care Act to help achieve the 3-part goal of lower costs, improved care, and better health.⁵²

Summary

A historical reliance on clinical trials designed to achieve regulatory approval has led to many therapeutic breakthroughs in cancer pharmacotherapy that have significant internal validity for demonstrating efficacy. However, despite significant

advances in cancer therapeutics, treatment outcomes remain less than ideal when patients who do not meet the strict inclusion criteria identified in the clinical trial receive treatment with the drug, a problem compounded when physicians have insufficient evidence to guide personalized treatment regimens. Within the past few years, an emphasis on patient-centered research has emerged; this is an approach that not only provides data to support a formulary decision, but also one that generates data applicable to the individual patient. As the U.S. health care delivery system continues to reform and evolve, CER and patient-centered outcomes research will be used to generate the type of data required by patients to make informed decisions about how to most wisely invest their limited health care resources. CER and patient-centered outcomes will also inform the decision making of payers and plan administrators as they redesign the oncology pharmacy benefit in the face of ongoing innovation, rising utilization, and increased costs. Going forward, all new benefits must strike the appropriate balance between clinical efficacy and safety, patient expense and noncompliance, and improved treatment outcomes.

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Multiple Myeloma: Supportive Care Requirements and Coordination of Patient-Centered Care

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Patients with multiple myeloma are susceptible to the consequences of the disease or treatment.¹ Although innovative treatments have significantly prolonged 5- and 10-year relative survival through improved disease control,² increased survival often comes at the cost of an increased disease-related symptom burden and prolonged exposure to potentially toxic therapy.³ Disease-specific symptoms caused by proliferation of plasma cells (e.g., bone lesions, renal dysfunction, anemia) must be continually monitored and managed.^{4,5} These hallmark features, combined with symptoms associated with toxicities related to multiple myeloma therapy (e.g., immunosuppression), complicate the management of the disease and reduce the physical, emotional, and psychosocial well-being of patients, making supportive care a critical component of the therapeutic strategy.⁴

Therapeutic intervention in supportive care is ultimately driven by patient need; however, prevention and treatment of disease sequelae such as bone disease and hypercalcemia, renal dysfunction, infection, and anemia take priority because if left untreated they may lead to organ system failure.⁶ Supportive care also frequently includes interventions to manage pain and coagulatory dysfunction (e.g., thrombotic disease, hyperviscosity).⁴ These interventions are briefly reviewed in the following text.

Bone Disease

Bone disease and its related hypercalcemia are hallmarks of multiple myeloma.⁷ Bone disease appears both as a diffuse loss of bone mass (osteoporosis) and well-defined focal lesions;⁸ at diagnosis, 70% of patients present with osteolytic lesions, and 30% have fractures.⁹ These manifestations of bone involvement can have deleterious clinical effects by increasing the morbidity associated with the disease. In addition, patients with multiple myeloma who develop fractures have a 20% increased risk of death.¹⁰

Osteolytic lesions—literally, holes in the bone—result from increased bone resorption (bone breakdown) due to stimulation of osteoclast activity that occurs in close proximity to myeloma cells.⁷ This process decreases bone mineral density and increases the risk of fractures.¹¹ Initially, some patients show both increased bone degradation and elevated osteogenesis (bone formation), but as the disease progresses, bone degradation far outweighs bone formation.¹² Patients with myeloma bone disease are susceptible to fractures occurring either spontaneously or following trivial injury. These pathological fractures most commonly involve the vertebrae, ribs, and long bones but occasionally occur in other sites such as the sternum and pelvis.⁹

To counter increased osteoclastic activity and bone resorption, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend that all patients with symptomatic disease receive bisphosphonate therapy.¹³ Renal function should be routinely assessed in patients treated with bisphosphonates and should be monitored for osteonecrosis of the jaw.¹³ Bisphosphonates may be considered for the approximately 15% of patients with asymptomatic (smoldering) disease,¹⁴ but current evidence does not support a broad recommendation for their use in these patients, and the NCCN recommends bisphosphonate treatment only as part of a clinical trial.¹³ In these patients, a skeletal survey should be conducted each year or when clinically indicated.¹³

Bisphosphonates approved for the treatment of bone loss in patients with multiple myeloma include 2 high-potency intravenous drugs: pamidronate and zoledronic acid.¹³ Two large, double-blind, randomized, placebo-controlled trials demonstrated that intravenous pamidronate administered monthly compared with placebo decreased pain and associated bone-related complications, improved performance status, and preserved quality of life in patients with advanced multiple myeloma.^{15,16} Compared with pamidronate, zoledronic acid is more potent, can be administered more rapidly, and has equivalent efficacy.¹⁷

The Medical Research Council (MRC) Myeloma IX Study examined the effects of prolonged treatment with intravenous zoledronic acid and oral clodronic acid (not approved in the United States) in patients with multiple myeloma, regardless of whether they had bone disease.¹⁸ Zoledronic acid was superior in reducing skeletal events, significantly improved progression-free survival, and extended median overall survival by 5.5 months, suggesting that intravenous zoledronic acid has an antimyeloma effect and improves bone integrity. However, intravenous zoledronic acid was also associated with a higher rate of confirmed osteonecrosis of the jaw, a rare adverse effect of long-term bisphosphonate therapy observed in patients with multiple myeloma,¹⁹ than oral clodronic acid (4% vs. 1%).¹⁸ Similarly, a single-center study that compared treatment of myeloma bone disease with either zoledronic acid or pamidronate reported that zoledronic acid was associated with a 9.5-fold greater risk than pamidronate for the development of osteonecrosis.²⁰ Because of the lower risk for drug-related osteonecrosis, pamidronate is the preferred bisphosphonate.¹³ However, the NCCN recommends that all patients with multiple myeloma receiving bisphosphonates be monitored for osteonecrosis of the jaw.¹³

The mechanism of bisphosphonate-induced osteonecrosis is unclear. However, periodontal disease, dental surgery, prior

TABLE 1 Adult Immunization Schedule Recommended by the Centers for Disease Control and Prevention by Vaccine and Age Group for 2012

Vaccine	Age (Years)					
	19-21	22-26	27-49	50-59	60-64	≥65
Influenza	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years					Td/Tdap
Varicella	2 doses					
Human papillomavirus (female)	3 doses					
Human papillomavirus (male)	3 doses	3 doses				
Zoster					1 dose	
Measles, mumps, rubella (MMR)	1 or 2 doses			1 dose		
Pneumococcal (polysaccharide)	1 or 2 doses					1 dose
Meningococcal	1 or more doses					
Hepatitis A	2 doses					
Hepatitis B	3 doses					

Key

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection.	Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications).	Tdap recommended for ≥65 years if contact with <12-month-old child. Either Td or Tdap can be used if no infant contact.	No recommendation.
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Adapted from: Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States—2012.⁵¹

trauma, corticosteroid therapy, immunocompromised state, vascular insufficiency, and hypercoagulability have all been implicated as possible etiologic or precipitating factors.²¹ Based on these observations, it is currently recommended that all patients undergo a comprehensive dental examination and cleaning before initiating treatment with intravenous bisphosphonates.²¹ If oral surgery is required during therapy, bisphosphonates should be discontinued at least 1 month before and for 3 months after the surgery or until healing is complete.²¹

Hypercalcemia associated with the increased bone resorption commonly observed in multiple myeloma occurs in 30%-40% of patients at some time during the course of the disease.¹ Hypercalcemia causes nausea, headache, and lethargy and contributes to polyuria, osmotic polydipsia leading to renal dysfunction, and renal stone formation.¹ Treatment for hypercalcemia is directed toward lowering the serum calcium concentration and increasing urinary calcium secretion or decreasing gastrointestinal calcium absorption. Recommended treatment includes hydration combined with furosemide, bisphosphonates, corticosteroids, and/or calcitonin. Among the bisphosphonates, the NCCN recommends short-term treatment with zoledronic acid for the treatment of hypercalcemia.¹³ Current data suggest that concerns about osteonecrosis of the jaw associated with zoledronic acid are of limited relevance in the management of acute hypercalcemia.¹⁷

Renal Dysfunction

Renal dysfunction is a common presentation in multiple myeloma and is seen in up to one-half of patients.¹ Advanced

renal failure is estimated to occur in 25% of cases. Renal dysfunction occurs not only as a consequence of multiple myeloma but secondary to treatment.¹³ To reduce the risk of renal dysfunction, hydration should be maintained and nonsteroidal anti-inflammatory drugs should be avoided. Intravenous contrast media used in conjunction with a computed tomographic scan should be avoided as well. Renal function in patients receiving bisphosphonates should be monitored, and in patients presenting with a creatinine clearance level less than 30 milligrams per deciliter (mg/dL), the dose should be reduced.¹³

Infection

Recurrent infections cause significant morbidity and are the leading cause of death in patients with multiple myeloma.⁴ Patients with multiple myeloma have approximately a 15-fold increase in the risk of infection, and an estimated 10% of patients die of infective disease within 60 days of diagnosis.²² Common infections are respiratory tract infections from *Streptococcus* and *Staphylococcus* and urinary tract infections due to *Escherichia coli*.¹ When receiving treatment, patients are at increased risk for viral and fungal infection due to the interplay of defective immunoglobulin production and the use of systemic corticosteroids and other medications for the treatment of multiple myeloma that suppress lymphocyte production.¹

During neutropenic periods, the NCCN recommends use of prophylactic antibacterial, antifungal, and antiviral agents to prevent the development of infections.¹³ In patients receiving high-dose dexamethasone therapy, prophylactic doses of antimicrobial agents are recommended to prevent *Pneumocystis*

carinii pneumonia, herpes, and fungal infections.¹³ During bortezomib therapy and following allogeneic hematopoietic cell transplantation, herpes zoster prophylaxis with antiviral agents is recommended.¹³ In the setting of recurrent, life-threatening infections, the NCCN recommends considering intravenous immunoglobulin therapy.¹³ However, immunoglobulin therapy is not without its challenges, including risk of infusion reaction, a relatively short duration (3-4 weeks) of action, and potential for supply shortages.¹³

The NCCN recommends that all patients with multiple myeloma be considered for routine immunization against influenza and pneumococcal infections.¹³ Immunizations for all adults in the United States currently recommended by the Centers for Disease Control and Prevention are highlighted in Table 1. There are 4 important caveats to routine immunization of patients with multiple myeloma: (a) vaccines should be administered 2 weeks before therapy; (b) a herpes zoster vaccine should not be administered to patients with a history of multiple myeloma; if the herpes varicella vaccine is required, it should only be administered when the patient is determined to be immunocompetent; (c) vaccines containing live viruses should be avoided until the patient is considered immunocompetent; and (d) because the immunosuppressive nature of multiple myeloma may prevent an appropriate response to the tuberculosis skin test (Mantoux), these patients may require a tuberculosis blood test (interferon gamma release assay).^{23,24}

Anemia

Anemia, defined as a hemoglobin level less than 12 grams per dL(g/dL), is present in approximately 75% of patients with multiple myeloma at diagnosis.²² In most patients with multiple myeloma, mean corpuscular volume is normal, and the anemia is due to decreased production of red blood cells ("normocytic anemia") attributed to the myeloma itself and/or the myelosuppressive effect of therapy.²⁵ If patients have mild to moderate anemia (defined as a hemoglobin level between 8 and 10 g/dL) and are asymptomatic, no treatment is recommended.²⁶ If patients are symptomatic from anemia caused by multiple myeloma, chemotherapy is indicated.²⁶ Anemia can also be managed by replacing red blood cells via transfusion or treatment with erythrocyte-stimulating agents (ESAs). Blood transfusion may be helpful for the short-term correction of moderate to severe anemia in a symptomatic individual. Given the increased risk of mortality, possible cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence with ESAs, the NCCN recommends limiting use of ESAs to patients on chemotherapy with their informed consent. Further, the U.S. Food and Drug Administration recommends concomitant administration of prophylactic anticoagulation,²⁷ and if ESAs are used, they should be prescribed at the lowest effective dose.²⁸

Pain

Pain, particularly pain in the skeleton, is a significant cause of morbidity in multiple myeloma, and 70%-80% of patients present with moderate to severe pain in the skeleton as a predominant symptom.^{1,4} Pain is often an indicator of relapse or progressive disease.²⁹ Typically, the pain is localized and unremitting, but it may be multifocal or migratory and can fluctuate in intensity.³⁰ Bone pain can emanate from several sources. Fractures of vertebral bodies, ribs, pelvis, or long bones are associated with an intense pain that suddenly occurs.³⁰ Pain can also result from irritation of sensory nerves caused by release of inflammatory cytokines in response to the disease process. Other sources of pain include neuropathy, nerve compression, infection, ulcerations, and adverse reactions to cytotoxic treatments.⁴

Pain management options have increased in recent years, allowing use of multimodality strategies. Strategies such as evidence-based pharmacologic therapies, percutaneous stabilization of vertebral fractures, localized radiotherapy, and physical therapy give patients and their providers several treatment options.^{4,6} The opioid class of analgesics remains the cornerstone of pharmacologic treatment for skeletal pain.⁴ In many cases, these agents fail to provide the necessary degree of pain relief, so a synergistic agent such as an anticonvulsant or antidepressant is added to enhance the opioid effect and diminish dose-related adverse effects. Nonsteroidal anti-inflammatory drugs can potentiate renal dysfunction in patients with multiple myeloma and are often avoided.⁴

For patients with pain from a plasmacytoma or a compression fracture, low-dose radiation therapy (10-30 Gy) is used for palliative treatment.¹³ Vertebroplasty and kyphoplasty are an alternative to radiation and are minimally invasive procedures involving the injection of cement to stabilize a vertebral fracture and rebuild a percentage of the vertebral height, thereby decreasing the pressure of the compression fracture.^{1,6} Physical support such as braces and physical/occupational therapy may also be used to minimize pain and allow daily activity to continue.³¹

Peripheral neuropathy, defined as damage to or degeneration of peripheral nerves, affects both sensory and motor pathways and can occur as a disease- and treatment-related complication in multiple myeloma; it usually presents as numbness, weakness, or burning pain.³² The reported incidence is 1%-20% in untreated patients and 35%-83% in patients treated for multiple myeloma.³³ The severity of the neuropathy ranges from mild to debilitating and has a substantial impact on patient quality of life.³³ Disease-related neuropathy occurs secondary to the multiple myeloma disease process or can be the result of compression of nerve roots.³² Risk factors for treatment-related peripheral neuropathy include duration of therapy, dose intensity, cumulative dose, and the presence of pre-existing neuropathy.³³ Comorbid conditions such as diabetes can also predispose patients with multiple myeloma to peripheral

neuropathy.³³ Older chemotherapies such as vincristine and platinum-containing agents are examples of drugs that cause treatment-related peripheral neuropathy.³⁴ Newer agents such as thalidomide and bortezomib are associated with sensory and motor neuropathies, some of which may be irreversible.⁶

Effective management of peripheral neuropathy can minimize the incidence and severity of its associated pain. Prevention is the preferred approach, and patients should be educated about the signs and symptoms of neuropathy and counseled to stop their medication if symptoms begin to appear.⁶ Early and regular monitoring with neurological evaluation and dose modification or treatment discontinuation as indicated is also recommended.³³ Few data exist to guide pharmacologic pain management in patients with multiple myeloma who have peripheral neuropathy, and most recommendations are based on case reports, personal experience, or application of clinical experience from other disease states (e.g., diabetic neuropathy).³² Recommended first-line agents include anticonvulsants (e.g., gabapentin, pregabalin) and antidepressants (e.g., nortriptyline, amitriptyline).³² Opioid analgesics and tramadol are recommended as second-line agents and anti-epileptics and ketamine as third-line therapies.³² Topical agents such as analgesic creams are effective when pain is localized to a specific area; however, topical applications offer little relief for patients experiencing numbness across multiple areas, such as the fingertips.³² It has been suggested that complementary therapy such as acupuncture can be used as an adjunctive therapy to reduce neuropathic pain; however, clinical data supporting this intervention in multiple myeloma are limited to case reports.^{35,36}

Coagulatory and Hematologic Dysfunction

There is a well-established association between cancer and coagulatory disorders such as venous thromboembolism (VTE) and hyperviscosity. Patients with multiple myeloma are at a higher risk for developing thromboembolic complications as a result of an impairment of both anticoagulant and fibrinolytic pathways, with at least 10% of patients developing VTE during the course of the disease.³⁷ Risk factors for VTE not specific to multiple myeloma include older age, obesity, tobacco use, infection, history of prior venous thromboembolism, use of ESAs, use of hormone replacement therapy, presence of a central venous catheter, and inactivity/immobility.³⁸ Disease-specific risk factors include monoclonal protein level greater than 1.6 g/dL, other signs of progressive disease such as increased production of inflammatory cytokines, and hyperviscosity.³⁸ Treatment with both thalidomide and lenalidomide further increase the risk of venous thromboembolism, particularly in newly diagnosed patients.¹³ When thalidomide and lenalidomide are used as a single agent in newly diagnosed patients, an estimated 3%-4% experience VTE. This risk increases to 14%-26% when thalidomide is combined with high-dose cortico-

steroids or multiagent chemotherapy and as high as 75% when lenalidomide is combined with a high-dose corticosteroid or chemotherapeutic agent.^{37,39-41}

Thromboprophylaxis is recommended for reducing VTE in patients receiving dexamethasone in combination with lenalidomide or thalidomide-based therapy.¹³ Various VTE prophylaxis strategies, such as low-molecular-weight heparin (LMWH), warfarin, or aspirin, have been investigated in small, uncontrolled clinical studies. To date, no study has clearly demonstrated a significant superiority of one prophylactic regimen over another. However, it appears as if aspirin is an effective prophylaxis for patients with ≤ 1 risk factor for VTE such as immobility, age, concomitant infections, hormone therapy, and a previous history of thrombosis.³⁷ LMWH (equivalent to enoxaparin 40 mg/day) is recommended for those with 2 or more individual/myeloma-related risk factors.³⁸ LMWH is also recommended for all patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin targeting a therapeutic international normalized ratio of 2-3 is an alternative to LMWH, although there are limited data in the literature with this strategy.⁴²

Hyperviscosity is rare in multiple myeloma, primarily affecting 2%-6% of patients with the immunoglobulin A and G subtypes of the disease.^{1,43} In hyperviscosity, the blood is resistant to flow due to the excessive amount of protein produced by the disease process. Complications commonly associated with hyperviscosity include mucous membrane bleeding, retinopathy, and neurologic and pulmonary symptoms.¹ The NCCN recommends plasmapheresis as an adjunctive therapy for patients with symptomatic hyperviscosity.¹³

Improving Care in Patients with Multiple Myeloma

Due to the clinical complexity of multiple myeloma, patients require care from numerous specialties, including hematology, radiation oncology, surgical oncology, specialty pharmacies, pain management, physical therapy, palliative care, and a host of other medical and nursing specialties. Treatments targeted at the disease activity as well as those provided as part of a supportive care regimen are necessary at all stages of the disease. In many instances, care delivery is fragmented and often poorly coordinated.⁴⁴ Coordinated, collaborative health care delivery improves clinical and patient-reported outcomes through interdependent decision making among multiple professionals.⁴⁵ Use of collaborative care has begun to be used in the context of cancer but at this time is relatively limited.⁴⁶

New models of collaborative care designed to facilitate clinical integration and collaboration between provider groups, improve coordination of care, enhance communication, and boost provider accountability while maintaining a focus on patient needs are emerging. The oncology patient-centered medical home is an example of an innovative model of care.⁴⁷ Providers delivering care within the oncology patient-centered

medical home proactively engage with patients to manage symptoms and look for disease progression over time, thus reducing acute events and decreasing resource utilization while improving outcomes. Medical homes also encourage utilization of interdisciplinary health care teams to deliver consistent and safe care.⁴⁸ Although the concept of specialty medical homes is in its infancy and individual practices must determine if reimbursement is available for delivery of medical home services,⁴⁹ there are examples of oncology practices implementing elements of this care delivery model. In partnership with the largest payer in California, the Wilshire Oncology Group transformed itself into a patient-centered medical home.⁵⁰ The re-engineering process was driven by a desire to provide a patient-centered approach, guideline-based therapy and supportive care, interval-based care, dignified end-of-life care, transparent data reporting, and quality measure validation.

A key to the transition was implementation of an oncology-specific electronic medical record (EMR) system that allowed the practice to track all provider-patient interactions and quantify the clinical and economic impact of care-oriented decisions. Use of an EMR improved patient care in this pilot program by prompting correct decision making at the time of care and recording disease and patient details, warranted variations, symptoms and their management, triage and interval care, as well as end-of-life care. A component of the EMR also allowed patients to fill out standardized reports and surveys. After 1 year, the medical home program was on track to reduce costs and improve clinical outcomes and patient satisfaction.⁵⁰

Summary

Multiple myeloma is a complex disease, and supportive care is essential to enhancing long-term outcomes and improving quality of life. In addition to treatments that directly target the disease process, patients with multiple myeloma frequently require management of several disease-related complications, including bone disease, renal dysfunction, infection, anemia, pain, and coagulopathy dysfunction. Bisphosphonates have been shown to reduce skeletal-related events and are well tolerated, but preventive steps should be taken to avoid renal impairment and osteonecrosis of the jaw. Hypercalcemia should be treated immediately with intravenous hydration, bisphosphonates, and other agents. Prophylaxis of infections should be considered, particularly in patients with a high tumor burden, receiving specific chemotherapeutic agents, and with a history of unusual infections. When infections occur, they should be treated aggressively. Symptomatic anemia should be treated with chemotherapy, red blood cell transfusion, and/or erythropoietic growth factors, depending on the cause of the anemia and with the patient's understanding of the risks of each approach. Adequate pain control via pharmacologic or radiotherapeutic intervention is critical to maintain quality of life. Thromboprophylaxis is recommended for patients at risk

for VTE, particularly those treated with dexamethasone in combination with lenalidomide or thalidomide-based therapy. The delivery of care to patients with multiple myeloma has historically been fragmented and hindered by poor communication, lack of coordination, and minimal accountability. New models of care designed to encourage clinical integration, improve communication, and enhance coordination of care are emerging.

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Oncology Pharmacy Management and the Evolving Role of Managed Care: Recommendations for a Changing Environment with a Focus on Multiple Myeloma

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CPE credit for this activity. During the period October 1, 2012, through October 31, 2013, participants must (a) read the learning objectives and faculty disclosures; (b) study the educational activity; (c) complete the post-test with a score of 70% or better; and (d) complete the evaluation.

Posttest Questions: Oncology Pharmacy Management and the Evolving Role of Managed Care: Recommendations for a Changing Environment with a Focus on Multiple Myeloma

1. Lenalidomide and bortezomib were granted regulatory approval based on a predicted improvement in survival using which surrogate endpoint?
 - A. Complete response
 - B. Partial response
 - C. Disease-free survival
 - D. Time-to-progression
2. Which of the following is not considered a marker of clinical benefit in patients with multiple myeloma?
 - A. Complete response
 - B. Progression-free survival
 - C. Disease-free response
 - D. Very good partial response
3. Which of the following is a key feature of successful management of patients with multiple myeloma?
 - A. Use of a clinical pathway
 - B. Off-label drug use when necessary
 - C. A buy-and-bill drug benefit
 - D. Wide variation in treatment, depending on the individual patient's needs
4. The assessment of a medical intervention against alternative interventions with the intent of identifying treatment approaches that are most likely to have preferable benefit-risk profiles or are considered cost-effective in real-world clinical settings is an assessment of _____.
 - A. Indirect treatment comparison
 - B. Network meta-analysis
 - C. Patient-centered outcomes research
 - D. Comparative effectiveness research
5. Which key stakeholder group is increasingly regarded as influencing access to and reimbursement for drug therapies?
 - A. Clinicians
 - B. Patients
 - C. Payers
 - D. Regulators

**Posttest Questions: Oncology Pharmacy Management and the Evolving Role of Managed Care:
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6. Which of the following should be considered for a successful oncology pharmacy management strategy?
 - A. Case management
 - B. Incentive programs
 - C. Patient support programs
 - D. All of the above
7. Included as part of the federal health reform passed by Congress in 2009, _____ will assume full responsibility for meeting a proposed 65 quality measures involving prevention, diagnosis, treatment, management, and aftercare of chronic illnesses.
 - A. A community health team
 - B. A health care innovation zone
 - C. An accountable care organization
 - D. A medical home
8. Patients with multiple myeloma may require supportive care for which of the following conditions?
 - A. Anemia
 - B. Renal dysfunction
 - C. Infection
 - D. All the above
9. All patients diagnosed with symptomatic multiple myeloma should receive which of the following classes of medications?
 - A. Bisphosphonates
 - B. Anticoagulants
 - C. Calcium channel blockers
 - D. Selective serotonin reuptake inhibitors
10. Anemia can be managed by replacing red blood cells via blood transfusion or treatment with _____.
 - A. Bisphosphonates
 - B. Chemotherapy
 - C. Dexamethasone
 - D. Erythrocyte-stimulating agents
11. Treatment with which of the following medications is a risk factor for venous thromboembolism?
 - A. Doxorubicin
 - B. Dexamethasone
 - C. Melphalan
 - D. Vincristine
12. The _____ provides an efficient and timely platform to communicate the treatment plan to the care team.
 - A. Collaborative care team meeting
 - B. Electronic medical record
 - C. Health care innovation zone
 - D. Oncology patient-centered medical home

**Evaluation Form: Oncology Pharmacy Management and the Evolving Role of Managed Care:
Recommendations for a Changing Environment with a Focus on Multiple Myeloma**

Postgraduate Institute for Medicine is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

	After participating in this activity, I am now better able to:				
Learning Objectives					
Review indicators of treatment outcomes for multiple myeloma	1	2	3	4	5
Demonstrate the use of comparative effectiveness research as a decision support tool to appropriately invest resources and reduce treatment variability with multiple myeloma therapies	1	2	3	4	5
Recommend methods to improve patient outcomes with supportive care for multiple myeloma within a health plan setting	1	2	3	4	5
Evaluate innovative oncology pharmacy benefit models and specialty management services	1	2	3	4	5
Provide accurate and appropriate counsel as part of the managed care treatment team	1	2	3	4	5

Based upon your participation in this activity, choose the statement(s) that apply:

- ☐ I gained new strategies/skills/information that I can apply to my area of practice.
- ☐ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice?

What barriers do you see to making a change in your practice?

**Evaluation Form: Oncology Pharmacy Management and the Evolving Role of Managed Care:
Recommendations for a Changing Environment with a Focus on Multiple Myeloma**

Which of the following best describes the impact of this activity on your performance?

- ☐ I will implement the information in my area of practice.
- ☐ I need more information before I change my practice behavior.
- ☐ This activity will not change my practice, as my current practice is consistent with the information presented.
- ☐ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

<i>The content presented:</i>					
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Promoted improvements or quality in health care	1	2	3	4	5
Was scientifically rigorous and evidence-based	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Would you be willing to participate in a post-activity follow-up survey?

- ☐ Yes
- ☐ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

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Supplement