SUPPLEMENT TO
MANAGED Care

Hematologic Cancer As a Chronic Disease

Shifting the Methodology and Impacting Cancer Care Management

Based on a satellite symposium at the Academy of Managed Care Pharmacy 20th Annual Meeting & Showcase San Francisco, April 18, 2008

HIGHLIGHTS

Myelodysplastic Syndromes

- Epidemiology and Pathophysiology
- Clinical Features and Diagnostic Evaluation
- Treatment Guidelines

Multiple Myeloma

- Pathogenesis and Symptomatology
- Initial Treatment Considerations
- Transplantation, Maintenance Therapy, and Relapse

Policy and Appropriate Patient Care

- Changes to Medicare Parts A, B, C, and D

This activity is sponsored by The Chatham Institute

The Chatham Institute

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

Celgene

Volume 17, No. 7
Supplement 6
July 2008

MANAGED Care

Editor
JOHN MARCILLE

Managing Editor
FRANK DIAMOND

Associate Editor
TONY BERBERABE

Design Director
PHILIP DENLINGER

MediMedia Managed Markets Publishing

Editor, Custom Publications
MICHAEL D. DALZELL

Senior Editors, Custom Publications
KATHERINE T. ADAMS
AMY KRAJACIC

Contributing editors to this supplement
SCHUYLER MATTHEWS
SUSAN L. WORLEY

Group Publisher
TIMOTHY P. SEARCH, RPH

Director of New Product Development
TIMOTHY J. STEZZI

Eastern Sales Manager
SCOTT MACDONALD

Senior Account Manager
KENNETH D. WATKINS, III

Director, Production Services
WANETA PEART

Circulation Manager
JACQUELYN OTT

MANAGED CARE (ISSN 1062-3388) is published monthly by MediMedia USA, 780 Township Line Road, Yardley, PA 19067. This is Supplement 6 to Vol. 17, No. 7. Periodicals postage paid at Morrisville, Pa., and additional mailing offices. POSTMASTER: Send address changes to MANAGED CARE, 780 Township Line Road, Yardley, PA 19067. Price: $10 per copy, $100 per year in the United States; $120 per year elsewhere. E-mail: editors_mail@managedcaremag.com. Phone: (267) 685-2788.

www.managedcaremag.com

INTRODUCTION

Managed Care Considerations: Hematologic Cancer as a Chronic Disease

RONNIE J. DEPUE, RPH
Corporate Clinical Pharmacy Director, Coventry Health Care, Glen Allen, Va.

With the development of targeted therapeutics and other novel treatments, the oncology landscape has changed enormously. Perhaps some of the greatest changes have taken place in the realm of the hematologic cancers. Less than a decade ago, patients diagnosed with diseases such as myeloma or one of the myelodysplastic syndromes (MDS) received a rather grim prognosis. Today, with the availability of multiple therapeutic regimens, patients with these disorders are living longer. In fact, many hematologic cancers are now perceived as chronic diseases – and this development has certainly gotten the attention of managed care.

A vast number of agents from existing and novel therapeutic categories have shown promise in improving survival rates compared with previously available agents. However, these newer agents are likely to be associated with higher treatment costs, more complicated administration, and the need for increased patient monitoring and education. Appropriate analyses are necessary to determine the place of these therapies in managed care. Because many of the newer agents are categorized as specialty pharmaceuticals and are covered by both medical and pharmaceutical benefits, MCOs have a unique opportunity to make improvements across the whole spectrum of care. At the same time, however, there is an industrywide need to shift from a medical style of management to a more rigorous pharmacy style of utilization management.

This management style brings safety, efficacy, and cost into sharper focus to develop the best coverage policies possible for the appropriate use of new agents. Considerations that play a role in utilization management include U.S. Food and Drug Administration-approved indication(s), along with recognition in the compendia and treatment guidelines. Data from the outcomes and safety profiles of different regimens, and determinations of whether agents are more appropriately used in a first- or a second-line setting also are invaluable. Another significant issue — patient compliance — can be affected by a number of variables that distinguish different therapies, including side effects, route of administration, and the level of beneficiary cost sharing. Finally, issues of cost reduction will remain at the forefront. In general, the goals are to start patients on the appropriate therapy, ensure compliance, and when appropriate, aim for remission.

In the following pages, a distinguished panel of experts reports on hematologic cancers, as well Medicare policies relevant to their management. Steven Coutré, MD, reviews MDS, Joseph M. Tuscano, MD, presents an overview of multiple myeloma, and Richard Stefanacci, DO, provides recent updates on related Medicare policies.

Disclosure: Ronnie J. DePue, RPh, reports no real or apparent conflicts of interest with respect to companies or other organizations or proprietary products mentioned in this article.

SUPPLEMENT TO
MANAGED Care

July 2008

Hematologic Cancer as a Chronic Disease:

Shifting the Methodology and Impacting Cancer Care Management

Based on a satellite symposium held at the Academy of Managed Care Pharmacy 20th Annual Meeting & Showcase, San Francisco, April 18, 2008

A Continuing Education Activity

This supplement is supported by an educational grant from Celgene Corp. The material in this supplement has been independently peer reviewed. The grantor played no role in reviewer selection.

SELF-STUDY CONTINUING EDUCATION ACTIVITY

Hematologic Cancer as a Chronic Disease

A statement of credit is offered to healthcare professionals who read pages 3 through 19 of this publication and submit the assessment and evaluation form on page 20. CME and CPE credit are offered. Estimated time to complete this activity is 2 hours. A statement of credit will be awarded upon successful completion of assessment questions (70 percent or better). If a score of 70 percent or better is not achieved, no credit will be awarded, and the registrant will be so notified. There is no fee for this activity.

Target audience

This program is targeted to medical directors, clinical and managed care pharmacists, and other health care decision makers in MCOs, health systems, academia, and industry.

Overview/needs assessment

Innovative approaches to cancer treatment are profoundly changing the management of many types of cancer. A host of new therapies with novel mechanisms of action are improving survival and are reducing morbidity, thereby shifting certain cancers into the chronic disease category. With these important advances in cancer care, MCOs will need to develop tools, processes, and analytics to manage these patient populations in optimal fashion.

This publication will focus on practical issues and challenges in the management of hematologic malignancies, including multiple myeloma and myelodysplastic syndromes. This program also will provide updates on treatment options that can be integrated into the treatment of patients with various hematologic malignancies.

Another important focus of this educational program will be CMS guidance with respect to clinical management of cancer patients and Medicare reimbursement policies in the arena of hematologic malignancies.

Educational objectives

After reading this publication, participants will be able to:

- Review clinical advances, including current and emerging therapeutics, and the epidemiology of hematologic cancers, specifically multiple myeloma and myelodysplastic syndromes.
- Discuss the components of the Medicare policy in the area of oncology.
- Assess best practices for cancer management within a managed care setting and the impact of the managed care pharmacist on patient care.

Accreditation and designation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the sponsorship of The Chatham Institute. The Chatham Institute is accredited by the ACCME to provide continuing medical education for physicians. The Chatham Institute designates this educational activity for a maximum of 2.0 *AMA PRA Category 1 Credits.*™ Physicians should claim credit commensurate with the extent of their participation in the activity.

The Chatham Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This program is approved for 2.0 contact hours (0.2 CEU) of continuing education for pharmacists.

ACPE Universal Program Number (UPN):
812-000-08-017-H01-P
Release Date: July 15, 2008
Expiration Date: July 15, 2009
Medium: Journal supplement

Planning committee members

Steven Coutré, MD; Joseph M. Tuscano, MD; Richard G. Stefanacci, DO, MGH, MBA, AGSF, CMD; Ronnie J. DePue, RPh; Chad Bertling, CE director, and Steven R. Peskin, MD, MBA, medical director, The Chatham Institute; Amy Krajacic, editor.

Conflict-of-interest policy and disclosures of significant relationships

It is the policy of The Chatham Institute to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. The Chatham Institute requires the disclosure of any significant financial interest or any other relationship a facility member may have with the manufacturer(s) of any commercial product(s) or device(s). Further, faculty members are required to disclose discussion of any off-label uses in their presentation. Any faculty members not complying with the disclosure policy are not permitted to participate in the educational activity.

Steven Coutré, MD, makes references to unlabeled/unapproved uses of lenalidomide in his article.

All program content has been peer reviewed for balance and any potential bias. Peer reviewers of this program have no real or apparent conflicts of interest to report with respect to the content of this publication. The process to resolve conflicts of interest aims to ensure that financial relationships with commercial interests and resultant loyalties do not supersede the public interest in the design and delivery of continuing medical activities for the profession.

The faculty of this program and the editorial staff of this monograph have disclosed the following:

Steven Coutré, MD: Honoraria from Novartis, Celgene, and Bristol-Myers Squibb, and consulting fees from Celgene.

Joseph M. Tuscano, MD: Honoraria from Amgen, Celgene, and Genentech.

Richard G. Stefanacci, DO, MGH, MBA, AGSF, CMD: Grant/research support from the American Society of Consultant Pharmacists, sanofi-aventis, Amgen, and Merck; and consulting fees from Celgene, NewCourtland Elder Services, Baxter Healthcare, Eisai, Pfizer, sanofi-aventis, Sepracor, Amgen, Merck, and Johnson & Johnson. He also serves on the speaker's bureau for Pfizer, Ortho McNeil, Abbott, GlaxoSmithKline, AstraZeneca, Forest Laboratories, Amgen, Merck, Daiichi Sankyo, Par, Eisai, and Schering-Plough, and the advisory boards for Pfizer, Eisai, Janssen, Solvay, Takeda, and Genentech.

Ronnie J. DePue, RPh; Steven R. Peskin, MD, MBA; Chad Bertling, CE director; and *Amy Krajacic, editor: No real or apparent conflicts of interest to report with respect to the content of this publication.*

Program sponsorship and support

This activity is sponsored by The Chatham Institute, and is supported by an educational grant by Celgene Corp.

Myelodysplastic Syndromes: Disease Overview and Therapy Options

STEVEN COUTRÉ, MD
Associate Professor of Medicine, Stanford University School of Medicine
Director, Hematology Clinic, Stanford Hospital and Clinic, Stanford, Calif.

SUMMARY

The increase in new cases of myelodysplastic syndromes is likely attributable to both an aging population and a greater number of cancer survivors who have received chemotherapy. A detailed diagnostic history is critical in order to place a patient in the proper treatment category.

Myelodysplastic syndromes (MDS) comprise a group of bone marrow disorders characterized by the underproduction of one or more types of blood cells. This impairment results in at least one of the hallmark chronic cytopenias associated with MDS — low blood counts reflected by anemia, thrombocytopenia, or neutropenia.


STEVEN COUTRÉ, MD

Epidemiology

According to the American Cancer Society (ACS), no registry was responsible for tracking the number of MDS cases until the National Cancer Institute recently assumed the task; thus, the exact number of cases found in the United States is currently impossible to ascertain. However, most estimates suggest that between 10,000 and 15,000 new cases are diagnosed each year (ACS 2007). The incidence of MDS, which increases with age, is approximately 5 per 100,000 individuals among the general population, and between 22 and 45 per 100,000 among those older than 70 (National Comprehensive Cancer Network 2008). Although MDS has yet to be given a firm ranking among similar diseases in terms of its relative frequency, with a prevalence of 30,000 to 40,000 in the United States, it is considered a somewhat common hematological disorder.

Although age is certainly a primary risk factor for MDS, the most important risk factor is prior treatment for cancer. Treatment with certain types of chemotherapy can significantly increase the risk of developing MDS, and the combination of chemotherapy and radiation therapy further heightens the risk. Smoking, already a known risk factor for acute myeloid leukemia (AML), also is likely to be a risk factor for MDS. A number of inherited diseases also have been linked to MDS, including Fanconi anemia, a rare inherited form of anemia that greatly increases the risk of developing both leukemia and MDS. Radiation and exposure to certain chemicals have been linked to MDS, and gender also is a slight risk factor, as MDS is somewhat more common among men than women.

Despite the multiple risk factors associated with MDS, the steady increase in the number of new cases in recent years most likely can be attributed to an aging population — more than 80 percent of patients are older than 60 — and an increasing number of cancer survivors who have received chemotherapy (ACS 2007).

Depending on the extent of disease and individual patient needs, the treatment of MDS can have significant economic implications. Although a thorough assessment of the economic burden of MDS has yet to be obtained, some cost estimates are available. A review of claims data for 336 transfusion-dependent patients with MDS that included total pharmacy costs and medical costs indicated that the average annual cost of treating such patients was almost $60,000 (Frytak 2007), with significant costs directly associated with transfusion. For patients, significant burdens in terms of reduced quality of life

Steven Coutré, MD, is an investigator for a number of protocols for hematologic malignancies. He is a published author and a nationally renowned speaker in the field of hematology. Coutré received his undergraduate degree from Northwestern University and his medical degree from Stanford University School of Medicine. His postgraduate training included a residency in Internal Medicine at Yale-New Haven Hospital, and fellowships in the Division of Hematology, and the Department of Microbiology and Immunology at Stanford.

(QoL) also are associated with anemia and the other cytopenias.

Pathophysiology

Ironically, despite the abnormally low blood counts that are the hallmark of MDS, this cluster of disorders often is characterized by an increase in the population of bone marrow precursor cells, or blasts, that give rise to red blood cells (RBCs), white blood cells (WBCs), and platelets. Aberrant stem cells divide rapidly and populate the bone marrow with dysplastic cells — cells that exhibit morphologic changes in the nuclei and cytoplasm, and that lead to significant bone marrow dysfunction. Not only do hematopoietic stem cells fail to differentiate properly in patients with MDS, but an increase in apoptosis, or programmed cell death, among healthy cells also occurs, further contributing to the cytopenias.

The initial cause of hematopoietic stem cell injury varies among patients, and may be a result of genetic mutations, cytotoxic chemotherapy, exposure to radiation or other chemicals, and/or viral infections. In some patients, a series of molecular defects, both genetic and environmental, may occur. It is postulated that cumulative mutations are required for the progression to AML (Nimer 2008).

Clinical features and diagnostic evaluation

A growing number of patients are diagnosed with MDS while they are still asymptomatic; in these patients, the disease is discovered because abnormal blood counts are found during a routine physical examination. However, in symptomatic patients, clinical features are almost always direct consequences of the cytopenias. Most patients with MDS have varying degrees of anemia, and more than half have significant anemia (hemoglobin <10). If symptomatic, these patients typically complain of fatigue, and may exhibit paleness or shortness of breath. Anemia can exacerbate symptoms associated with a number of comorbidities common among elderly patients, such as coronary artery disease or pulmonary disease, and, in some cases, it is a worsening of the comorbidity that causes the clinician to suspect anemia, and in turn, MDS. Patients with MDS also are at risk for a form of AML that often is refractory to standard treatment.

Approximately 40 percent of patients with MDS come to a clinician's attention because of a low WBC, or neutropenia. Neutropenia elevates the risk of contracting bacterial infections, such as pneumonia and urinary tract infections. In some cases, even patients who have not yet developed neutropenia experience recurrent infections; although WBC counts in these patients are normal, the functioning of these cells is impaired. Another 40 percent of patients with MDS present with a low platelet count, or thrombocytopenia; such patients have an increased tendency to bruise and bleed. Nosebleeds and bleeding of the gums, particularly after dental work, are common symptoms among these patients.

The diagnostic evaluation of a patient with MDS requires a detailed clinical history and assessment of clinical status, both of which play a role in placing a patient in the appropriate subcategory for prognosis and treatment. In addition to blood and reticulocyte counts, a peripheral blood smear is obtained to determine the degree of dysplasia exhibited by a patient's blood cells. A bone marrow examination is used to characterize the cytopenias, rule out differential diagnoses, and obtain a cytogenetic evaluation. Serum levels of erythropoietin (EPO), vitamin B12, ferritin, RBC folate, and iron also are typically obtained during initial evaluation and throughout treatment.

The IPSS scoring system

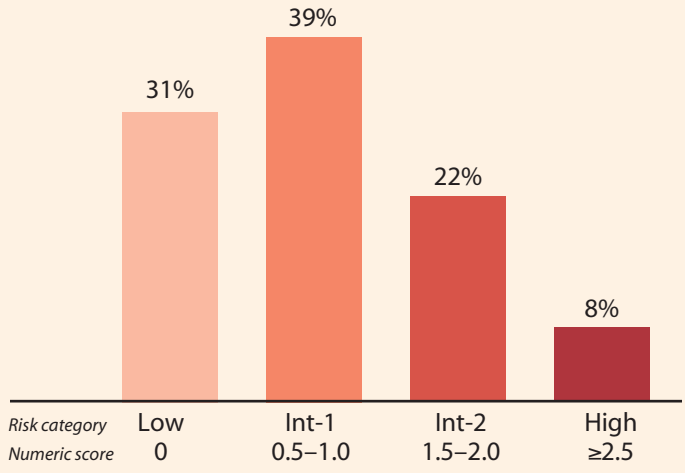
For over 25 years, various diagnostic criteria have been analyzed with the goal of developing a classification system useful for diagnosis, prognosis, and treatment implications for patients with MDS. Developed in 1997, the International Prognostic Scoring System (IPSS) has improved upon previous systems with regard to both clinical utility and usefulness in examining clinical trial results. In addition, recent changes in ICD-9 codes for MDS reflect the use of IPSS, and perhaps have helped to further endorse its categories.

Greenberg (1997) examined patient databases with the goal of identifying variables that predicted patient outcomes with the greatest degree of reliability. The group zeroed in on cytogenetics (karyotype), percentage of bone marrow blasts, and number of cytopenias as the variables with the greatest prognostic significance; next, they developed a system whereby they could assign points to each of these components based on their clinical impact, with a greater number of points indicating a less favorable prognosis. A patient's total IPSS score was then used to assign the patient to one of four groups: low risk; intermediate-1 risk; intermediate-2 risk; or high risk. Patients have been further classified as low/intermediate-1 risk or intermediate-2/high risk for treatment purposes, with such approaches for the latter group taking into consideration a greater risk among these patients for the development of acute leukemia. Patient distribution among IPSS risk categories is shown in the Figure.

Treatment guidelines

Transfusion with RBCs and platelets, along with antibiotic supportive care, continues to be the mainstays of treatment for patients with MDS. In addition, erythropoiesis stimulating agents (ESAs) and myeloid growth factors, such as granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), are now commonly used. More re-

FIGURE
IPSS risk categories: patient distribution



Int=intermediate, IPSS=international prognostic scoring system.
Source: Greenberg 1997

cently, the novel hypomethylating agents, decitabine (Dacogen) and azacitidine (Vidaza), and the immunomodulator lenalidomide (Revlimid) have been approved for use. Although these new agents represent therapeutic advances, their adoption may require clinicians to make more complicated treatment decisions when developing management strategies.

The guidelines developed by the National Comprehensive Cancer Network (NCCN) provide a good framework for understanding the disease, are widely recognized as representing the standard of care, and are useful in their application. The NCCN panel of experts endorses the use of IPSS risk categories and recommends treatments according to whether patients are assigned to either the low/intermediate-1 risk or intermediate-2/high-risk group. The NCCN recommends that all patients in the first group receive supportive care in addition to any treatment with disease-modifying agents. In the higher-risk group, patients are further stratified, depending on whether they are candidates for intensive therapy. Candidates for intensive therapy are at high risk for developing acute leukemia, but are young enough and have a good enough performance status to endure chemotherapy regimens and possibly transplantation. If patients are not candidates for such aggressive treatment, they may be candidates for the hypomethylating agents recently approved for this patient population. The NCCN also strongly encourages interested patients to participate in clinical trials, which help to improve outcomes for all patients.

ESAs. These agents often are an efficacious alternative to repeated RBC transfusions. As MDS evolves, refractory anemia, which occurs in a majority of patients, can result in a steady decline in hemoglobin and long-term dependence on packed RBC transfusions. Such transfusion dependence has been associated with iron overload and heart and liver complications, which can significantly reduce patient survival. Although their use is not without risk (NCCN 2008), ESAs may reduce the need for transfusion, raise hemoglobin levels, and improve QoL for patients who respond to therapy.

Until recently, perhaps the greatest drawback to the use of ESAs was the lack of proper criteria for determining the adequacy of an erythroid response (ER). However, in 2000, an International Working Group (IWG) proposed standardized criteria for evaluating clinically significant responses in patients with MDS; in addition to standardized measures of cytogenetic response and improvement in health-related QoL, the group proposed criteria for assessing hematologic improvement (Cheson 2000). The relevance of all IWG response criteria has been validated in clinical trials, and has gained acceptance both in research studies and clinical practice. The standardized criteria for determining ER also have — perhaps inadvertently — helped to confirm the usefulness of ESAs such as EPO.

A systematic review of data from 21 studies of patients with MDS who were treated with EPO has been instrumental in obtaining support for the use of IWG criteria for ER (Moyo 2006). The studies were published between 1990 and 2005 and evaluated 895 patients. The primary aim of the review was to analyze study characteristics that affected ER rate and determine possible explanations for between- and within-study variations. Ten studies (combined 604 patients) used the IWG criteria to define ER and 11 studies (291 patients) used other definitions (Moyo 2006). The mean age of all patients was 70.6 years, and 45 percent were women. Mean baseline serum EPO levels and the proportion of patients with refractory anemia were comparable between studies; however, the proportion of transfusion-dependent patients at baseline was lower in the IWG studies compared with the non-IWG studies (36 percent versus 84 percent, respectively, $P<.001$). Overall, significantly higher ER rates occurred in studies that used IWG criteria. Among patients in the IWG studies who achieved an ER, 62 percent (188/305) achieved a major ER. Findings also were more consistent among the IWG criteria studies, suggesting that IWG criteria represent a more refined definition of ER and, in turn, use of the IWG criteria represents an improvement in the management of anemia.

This meta-analysis that involved an elderly population who were significantly anemic also helped to confirm that treatment with EPO is most effective in patients

whose serum EPO level is below 500 mU/mL. Some patients may derive additional benefit when EPO is combined with growth factors that stimulate the bone marrow to produce WBCs; this combination may result in a synergistic erythroid effect. The combination of EPO and G-CSF appears to be most beneficial for patients in the IPSS low-risk or intermediate-1 risk group.

Darbepoetin. A major change to the NCCN guidelines in 2007 involved the addition of darbepoetin alfa (Aranesp) as a recommended alternative to EPO for anemic patients with low/intermediate-1 risk MDS. Darbepoetin is a related but longer-acting form of EPO; it requires only once-weekly dosing, compared with EPO, which may require dosing as often as three times a week. As with EPO, darbepoetin is most effective in patients with low-risk MDS who have low blood serum EPO levels (<500 mU/mL). A number of studies indicate that darbepoetin is a relatively safe and well-tolerated treatment for anemia. Combined major and minor ER rates of 40 to 60 percent that were demonstrated in studies that used the IWG response criteria suggest that darbepoetin is an effective agent that may offer patients a significant QoL improvement (Musto 2005, Mannone 2004).

Clinical trials have suggested that overall response rates to darbepoetin are similar to and, in some cases, higher than response rates to EPO (Musto 2005, Stasi 2005). A meta-analysis of clinical trial results also found that higher initial doses of either agent and lower baseline serum EPO levels correlated with higher response rates among patients (Table). Findings from these studies suggest that appropriate patient selection is an important issue with regard to the use of ESAs. Neither EPO nor darbepoetin is recommended in patients with serum EPO levels above 500 mU/mL because such patients are unlikely to respond to either agent. In addition, all patients receiving ESAs should be monitored appropriately to ensure that these agents are discontinued in a timely fashion when they prove to be ineffective; currently, many patients continue to receive these agents even when they fail to produce a meaningful response.

Lenalidomide. Lenalidomide, an analogue of thalidomide, is part of a proprietary class of drugs called immunomodulatory drugs. It has both immunologic and pharmacologic effects that include cytokine- and immune-modifying properties, modulation of signals in the microenvironment that surrounds diseased clonal cells, and anti-angiogenesis. Lenalidomide's multiple mechanisms of action result in effective activity in patients with multiple myeloma as well as those with MDS. In the latter group, lenalidomide has additional effects, including enhanced EPO receptor signaling that restores effective erythropoiesis in normal and malignant stem cells. In patients with deletion of chromosome 5q, lenalidomide is directly cytotoxic and thus highly effective in suppressing aberrant precursor cells. Although lenalidomide has proven to be an effective agent for the treatment of MDS, its studies have generally focused on low and intermediate-1 risk MDS; conclusive data on lenalidomide's effectiveness in intermediate-2 or high-risk patients is not available.

Patients with chromosome 5q deletion. In 2005, the FDA approved the use of lenalidomide for the treatment of transfusion-dependent anemia in patients with IPSS-ranked low or intermediate-1 risk MDS with chromosome 5q deletion. This approval was based upon the results of a multicenter phase 2 study. This pivotal safety and efficacy study involved 148 patients with transfusion-dependent anemia and the 5q deletion, either with or without additional cytogenetic abnormalities (List 2006). The primary study endpoint was RBC-transfusion independence (TI) after completion of 24 weeks of treatment. Response was assessed using modified IWG response criteria. Lenalidomide was initially administered at an oral dose of 10 mg every 21 days in a 28-day cycle, and later was administered on a continuous dosing schedule. Secondary endpoints in the study included duration of ER, neutrophil and platelet responses, and cytogenetic response; data regarding safety also was obtained.

TABLE

Comparative meta-analysis of erythroid response rates for EPO and darbepoetin

Parameter	Darbepoetin studies	EPO studies	*P*
Erythroid response (%) (95% CI)	59.4 (49.0–69.9)	57.6 (45.1–70.0)	=.8282
Standard versus higher dose erythroid response rates (%)*	47.8 vs. 63.3	52.6 vs. 71.1	<.001

CI=confidence interval, EPO=erythropoietin.

*EPO standard dose ranged from 30,000 to 40,000 units, DARB standard dose was ≤150 mcg. EPO higher dose was 60,000 to 80,000 units, DARB higher dose was >150 mcg.

Source: Mundle 2006

In an intent-to-treat (ITT) analysis, 112 patients (76 percent) had a reduced need for transfusion by week 24, and 99 patients (67 percent) achieved TI, regardless of complexity of cytogenetic abnormalities (List 2006). The time to response was rapid (median, 4.6 weeks) and durable, with the majority of patients remaining transfusion-free after 1 year. Overall, 90 percent of patients who responded to treatment demonstrated evidence of response within 3 months of beginning lenalidomide treatment.

ER among patients was closely associated with cytogenetic response. A complete cytogenetic response occurred in 45 percent of patients, and 73 percent of patients experienced cytogenetic improvement. Most patients with cytogenetic response achieved TI, indicating a strong correlation between cytogenetic response and hematologic improvement.

The most common adverse event in this study was myelosuppression, which required treatment interruption or dose reduction in patients with moderate-to-severe neutropenia (55 percent) or thrombocytopenia (44 percent). Less common adverse events, including diarrhea, pyrexia, rash, and fatigue, were generally mild.

Patients without chromosome 5q deletion. Recent published results from a multicenter, phase 2 trial with a similar study design provided eagerly awaited information about the use of lenalidomide in patients without chromosome 5q deletion (Raza 2008). As with the previous trial, these participants were low/intermediate-1 risk, transfusion-dependent patients. The primary endpoint was TI (2 months without transfusions) and an increase in hemoglobin level.

Eligible patients had 50,000/mm^3 or more platelets and required two or more units of RBCs within the previous 8 weeks; 214 patients received either 10 mg oral lenalidomide daily or 10 mg on days 1 to 21 of a 28-day cycle with 7-day breaks. Using an ITT analysis, 56 (26 percent) patients achieved TI after a median of 4.8 weeks of treatment, with a median TI duration of 41.0 weeks; thus, as with patients with the 5q-deletion, the time to initial response was rapid. In patients who achieved TI, the median rise in hemoglobin was 3.2 g/L from baseline. A 50 percent or greater reduction in transfusion requirement occurred in 37 additional patients, resulting in an overall 43 percent rate of hematologic improvement. As with the previous trial, the most common grade 3/4 adverse events were neutropenia (25 percent) and thrombocytopenia (20 percent). Although TI occurred in a smaller number of patients compared with the previous trial, patient responses were rapid and durable.

These studies, which demonstrate that lenalidomide has clinically meaningful activity in transfusion-dependent patients with low- or intermediate 1-risk MDS, either with or without the 5q deletion, have prompted trials of lenalidomide in higher-risk patients with greater karyotype complexity. New studies are currently exploring the agent's potential in both higher-risk MDS and in elderly patients with AML, both with and without chromosome 5q deletion.

Hypomethylating agents. Hypomethylating agents have been a major focus of clinical research during the past few years. The two best-studied hypomethylating agents are the structurally similar analogs decitabine and azacitidine, both of which have been evaluated and approved for use in patients with advanced or high-risk MDS. Although these agents are typically used in patients who are not candidates for high-intensity therapy, the NCCN panel recently determined that they also are appropriate for patients with intermediate-2/high-risk MDS who may be candidates for intensive therapy but who lack an available donor for hematopoietic stem cell transplantation (NCCN 2008). Hypomethylating agents work by restoring the inactivation of tumor suppressor genes caused by aberrant DNA methylation in patients with MDS. These agents have been proven to inhibit DNS methylation, reactivate tumor suppressor genes, and trigger apoptosis in aberrant cells.

Azacitidine. Azacitidine, the first hypomethylating agent approved specifically to treat MDS, is administered by subcutaneous injection. In clinical trials, intermediate-2/high-risk patients treated with azacitidine had longer overall survival compared with patients who received best supportive care or conventional treatment (Fenaux 2007). In most trials, one subcutaneous injection of azacitidine was given daily for 7 days every 4 weeks. Patients had durable hematologic improvements, including increases in RBC counts and TI, increases in hemoglobin, increases in WBC or platelet numbers, and/or decreases in the percentage of bone marrow blasts (Silverman 2006). In some clinical trials, the time to onset of AML was significantly delayed in patients who were treated with azacitidine compared with patients who did not receive the agent (Silverman 2006). All patients in these clinical trials received supportive care regardless of whether they received azacitidine.

Alternative dosing of azacitidine has been explored both in clinical settings and in a number of clinical trials (Lyons 2008). Despite disease improvement with azacitidine, many patients with MDS find the frequent dosing schedule to be inconvenient. To determine whether alternative azacitidine regimens resulted in efficacy and safety comparable to 7-day regimens, Lyons conducted a phase 2, prospective, multicenter, open-label study to evaluate three different dosing schedules. Patients were randomized to receive 1 of 3 regimens for six 28-day cycles. A 2-day, no-treatment period was used in two arms to test the possibility of eliminating weekend dosing. In the first regimen, AZA-5, patients received azacitidine 75 mg/m^2/day for 5 days (n=50). In the second regimen, AZA-5-2-2, patients received azacitidine

75 mg/m^2/day for 5 days, followed by 2 days of no treatment and then 2 additional days of 75 mg/m^2/day (n=50). The third regimen, AZA-5-2-5, consisted of azacitidine 50 mg/m^2/day for 5 days, followed by 2 days of no treatment and then 5 additional days at the 50 mg/m^2/day dose (n=51). Hematologic improvements in all groups were comparable to those obtained with a 7-day schedule. TI was achieved in 16, 12, and 12 patients in the AZA-5, AZA-5-2-2, and AZA-5-2-5 arms, respectively. Approximately 63 percent of patients who were transfusion dependent at baseline achieved TI with treatment. No new adverse effects were reported with these alternative-dosing regimens; their efficacy and tolerability suggest that clinicians may have flexibility in designing new treatment regimens without weekend dosing.

Decitabine. Decitabine is another agent that strongly inhibits DNA methylation and has been proven to be clinically effective in patients with MLS (Saba 2005). Decitabine also is capable of inducing cell differentiation and has led to cytogenetic conversion in approximately 30 percent of patients (Lübbert 2001). In high-risk patients, response rates have been as high as 64 percent, and with regard to overall response rates, decitabine appears to exhibit efficacy comparable to that of azacitidine (Saba 2005).

The FDA has approved decitabine for use as an intravenous agent only in a hospital setting. However, as with azacitidine, alternative-dosing regimens have evolved over time in clinical practice. Some alternative regimens, such as using lower doses in an outpatient setting, have been evaluated in randomized trials. For example, Kantarjian (2007) has demonstrated optimal results with a 1-hour, 5-day schedule of decitabine use in an outpatient setting. As with azacitidine, longer treatment did not result in improved rates of survival.

Conclusion

Just a decade ago, patients with MDS had few treatment options outside of supportive care and transfusions. Today, an expanding list of approved agents, including erythropoietins (EPO and darbepoetin alfa), myeloid growth factors, such as G-CSF and GM-CSF, the hypomethylating agents decitabine and azacitidine, and lenalidomide have increased the rational treatment options available. With a considerable number of new agents demonstrating efficacy in phase 1 and 2 clinical trials, it is likely that some of the currently unmet needs among patients with MDS will be addressed in the coming years.

References

American Cancer Society. Overview: myelodysplastic syndrome. How many people get MDS. 2007. «http://www.cancer.org/docroot/CRI/content/CRI_2_2_1x_How_Many_People_Get_MDS_65.asp?rnav=cri.» Accessed June 2, 2008.

Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood.* 2000;96:3671–3674.

Fenaux P, Mufti GJ, Santini V, et al. Azacitidine treatment prolongs overall survival in higher-risk MDS patients compared with conventional care regimens: results of the AZA-001 phase III study. *Blood.* 2007;110:817.

Frytak JR, Henk HJ, de Castro CM, et al. Cost of transfusion dependency among managed care patients with myelodysplastic syndromes. *Clin Adv Hematol Oncol.* 2007;5(7):7–8.

Greenberg P, Cox C, LeBeau MM, et al. International scoring system (IPSS) for evaluating prognosis in myelodysplastic syndrome. *Blood.* 1997;89:2079–2088.

Kantarjian H, Garcia-Manero G, O'Brien S, et al. Survival and efficacy of decitabine in myelodysplastic syndromes (MDS), analysis of the 5-day IV dosing regimen. *Blood.* 2007;110:115.

List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355:1456–1465.

Lübbert M, Wijermans P, Kunzman R, et al. Cytogenetic responses in high-risk myelodysplastic syndrome following low-dose treatment with the DNA methylation inhibitor 5-aza-2'-deoxycitidine. *Br J Haematol.* 2001;14:349–357.

Lyons RM, Cosgriff T, Modi S, et al. Results of the initial treatment phase of a study of three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *Clin Adv Hematol Oncol.* 2008;5(7 suppl 10):8.

Mannone L, Gardin C, Quarre MC, et al. High response rate to darbepoetin alfa in "low risk" MDS: results of a phase II study. *Blood.* 2004;104:69a.

Moyo V, Lefebvre P, Duh MS, et al. Erythroid response (ER) rates in myelodysplastic syndromes (MDS) patients treated with epoetin alfa (EPO): a meta-analysis using the International Working Group criteria (IWGc) for MDS response. *J Clin Oncol.* 2006 June 20 Suppl. 2006 ASCO Annual Meeting Proceedings Part I. 24(18S):6572.

Mundle SD, Lefebvre P, Duh MS, et al. Erythroid response (ER) rates in myelodysplastic syndromes (MDS) patients treated with Epoetin Alfa (EPO) or Darbepoetin Alfa (DARB) using International Working Group criteria (IWGc): comparative metaanalysis. *Blood.* 2006;108: abstract 2672.

Musto P, Lanza F, Balleari E, et al. Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol.* 2005;128:204–209.

NCCN (National Comprehensive Cancer Network). NCCN Clinical Practice Guidelines in Oncology. Myelodysplastic Syndromes; v.2.2008. «http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf.» Accessed June 2, 2008.

Nimer SD. Myelodysplastic syndromes. *Blood.* 2008;111:4841–4851

Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood.* 2008;111:86–93.

Saba H, Wijermans PW. Decitabine in myelodysplastic syndromes. *Semin Hematol.* 2005;42:S23–S31.

Silverman LR, McKenzie DR, Peterson BL. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;20:3895–3903.

Stasi R, Abruzzese E, Lanzetta G, el al. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1–risk myelodysplastic syndromes. *Ann Oncol.* 2005;16:1921–1927.

Disclosures: Steven Coutré, MD, has received honoraria from Novartis, Celgene, and Bristol Myers Squibb, and a consulting fee from Celgene. He reports having been compensated for work related to lenalidomide (Revlimid).

Multiple Myeloma: Epidemiology and Therapeutic Options

JOSEPH M. TUSCANO, MD
Associate Professor of Medicine, Department of Internal Medicine, Division of Hematology and Oncology
University of California–Davis Cancer Center, Sacramento

SUMMARY

Myeloma remains an incurable disease, but its management has significantly improved with the introduction of novel treatment agents. Variations in both disease manifestation and patient response to treatment have personalized approaches to care.

Multiple myeloma (or simply myeloma) is an incurable cancer of plasma cells that results in significant disruption of the bone marrow microenvironment, along with the destruction and invasion of surrounding bone. This typically progressive disease currently accounts for approximately 10 to 20 percent of hematologic cancers and approximately 1 percent of all cancers (Ries 2007). As with most other hematologic cancers, it currently is regarded as a chronic incurable disease, although recently developed, highly effective therapeutics hold great promise for patients with this disease.

JOSEPH M. TUSCANO, MD

Epidemiology and pathogenesis

In the United States, the annual incidence of myeloma is approximately 4 cases per 100,000 individuals, and the American Cancer Society (ACS) estimates that there will be about 20,000 new cases of myeloma and more than 10,000 deaths from the disease this year (ACS 2008). In the United States, approximately 45,000 to 50,000 people live with this disease (ACS 2008).

The most significant risk factor for multiple myeloma is age; the median age at diagnosis is 70 and the disease is rarely diagnosed in individuals younger than 45 (Ries 2007). The current 5-year survival rate is estimated to be approximately 34 percent, with a significantly higher rate found among younger patients (ACS 2008). Survival rates for myeloma patients have been steadily increasing and this trend is expected to continue throughout this decade.

Myeloma is nearly twice as common among African Americans as European Americans, and more common in men than women (Ries 2007). Data also suggest that environmental factors, such as exposure to chemical toxins or ionizing radiation, may play a role in the development of this disease, as may immune system disorders (Durie 2007).

When myeloma was first identified, the disease was attributed to the malignant transformation of a single plasma cell, with related morbidity almost entirely the consequence of the uncontrolled growth of myeloma cells. Currently, the disease is more accurately characterized as a microenvironmental disorder. Research has shown that both the proliferation and survival of myeloma cells, along with their ability to develop resistance to various drugs, are greatly influenced by their immediate surrounding environment (Mitsiades 2007).

The microenvironment of surrounding myeloma cells consists of extracellular matrix proteins, bone marrow stromal cells (BMSCs), osteoblasts, osteoclasts, and various cytokines, among other components. The interaction of myeloma cells with BMSCs by means of adhesion molecules is of particular importance in the pathogenesis of myeloma; once myeloma cells adhere to BMSCs, chemical messengers and growth factors called cytokines are released, which stimulate the growth of myeloma cells and prevent apoptosis. The release of a variety of cytokines, most importantly interleukin (IL-) 6, also contributes to angiogenesis (the growth of new blood

Joseph M. Tuscano, MD, received his medical degree from the University of Southern California School of Medicine. He conducted his internship and residency at the University of California–Davis Medical Center, and had a fellowship in oncology at the National Institutes of Health. His specialty areas include bone marrow transplantation with high-dose chemotherapy for metastatic breast cancer, lymphoma, leukemia, testicular cancer, and multiple myeloma. He researches signal transduction, notably in human B-cell malignancies, and has identified a signal cascade implicated in chronic myelogenous leukemia. He also is looking at other proteins thought to affect lymphoma.

vessels that support the proliferation of myeloma cells), osteoclast activation (which interferes with normal growth and repair of bone), and several myeloma-related immunodeficiencies. Cytokines also activate intracellular signaling pathways that further enhance the expression of adhesion molecules, reinforcing a cycle of anti-apoptotic activity (Mitsiades 2007).

Symptoms and diagnosis

Myeloma cells produce monoclonal (M) proteins that interfere with normal bone remodeling and repair; thus, bone destruction is often a first indication of the disease, and the most common presenting complaint among patients is bone pain. Lytic bone lesions occur in almost 70 percent of patients, many of whom present with compression fractures in the spine and other areas. Anemia also is a common symptom, as is hypercalcemia, or the excess calcium in the blood that results from the resorption of bone. Kidney dysfunction frequently is caused by proteins secreted from myeloma cells, as well as by increased levels of calcium from bone resorption; renal failure is not unusual in patients with myeloma and is a poor prognostic factor. Patients also are at an increased risk for bacterial and viral infections for a variety of reasons, including reduced white blood cell count, inhibition of normal immunoglobulin production, impaired T-lymphocyte function, and eventually, as a result of treatment. Infection often accompanies the diagnosis, progression, and terminal stages of this disease.

The diagnostic evaluation of myeloma patients typically involves a list of tests. With the adoption of the International Staging System (ISS), introduced in 2005 to replace the more complicated Durie-Salmon system, fewer tests are required for definitive diagnosis and staging. However, many laboratory tests remain useful for monitoring the disease because of significant interpatient variations in its manifestation and response to treatment. Moreover, data analyses of the results of currently indicated tests may eventually be used to predict which patients will respond to a particular type of therapy.

A characteristic feature of most myeloma cells is their tendency to secrete M protein into the blood and urine; indeed, patients often are diagnosed with myeloma because this protein is discovered on routine assays before symptoms emerge. However, studies have shown that the amount of M protein secreted by myeloma cells varies considerably among patients; in fact, the lack of M protein excretion occurs in less than 10 percent of all patients (Kyle 2003). For each patient, a ratio of M protein to tumor burden must be established, and in some patients this ratio may change during treatment. More useful with regard to treatment implications is the identification of the particular subtype of monoclonal protein that is produced by a patient's myeloma cells (eg, IgG, IgA, IgD, or IgA). This information is obtained by immunofixation and may predict clinical behavior and prognosis, and most important, can be used as a tumor marker to monitor disease status.

The simplified diagnosis of myeloma begins with a bone marrow biopsy used to confirm the presence and number of myeloma cells. When these cells comprise less than 10 percent of all bone marrow cells, a patient is determined to have monoclonal gammopathy of undetermined significance (MGUS). The risk of transition from MGUS to myeloma is very low — only about 1 percent per year (Kyle 2002). When myeloma cells constitute between 10 and 30 percent of all bone marrow cells, and a patient has no other significant end-organ damaged (anemia, renal failure, etc.), he or she is classified as having indolent or smoldering myeloma. This asymptomatic form of the disease also is unlikely to rapidly progress to myeloma, but the risk for progression is higher — approximately 10 to 20 percent per year (Kyle 2007). Patients with inactive disease should be observed every 3 to 6 months (NCCN 2008). If signs of disease progression emerge (≥25 percent increase in M protein, evidence of lytic disease or hypercalcemia, or ≥50 percent increase in tumor volume in patients with plasmacytoma) patients should undergo treatment for active disease. There is no evidence that early treatment of these asymptomatic forms is advantageous (Rajkumar 2006a), but many of these patients do elect to participate in clinical trials to assess early treatment options.

Initial treatment considerations

One of the most important clinical challenges associated with the management of myeloma is determining the goal of treatment. Myeloma is an incurable disease and long-term complete remissions are relatively rare. Thus, although improving the complete response (CR) rate among patients is typically the goal in clinical trials, but under a physician's care, this may not always be practical, especially given a patient's functional status or comorbid conditions. Treatment must be tapered to fit the needs of each individual patient, with quality of life (QoL) serving as an important consideration.

No single treatment for myeloma presently is recognized as standard therapy. At every stage of treatment, clinicians encounter multiple options and generally choose from the same selection of agents. Significant patient variations require that clinicians draw on whatever information is available about the treatment of similar patients, with an ever-increasing focus on determining the optimum combination and sequencing of agents. To assist in decision making, the National Comprehensive Cancer Network (NCCN) compiles guidelines based on recommendations of an expert committee charged with reviewing existing clinical trial data and forming a consensus for treatment. These guidelines, published once a year, are the most comprehensive available.

The guidelines provide recommendations for all treatments and assign each to a category that indicates the level of agreement among committee members with regard to appropriate use. Category 1 is assigned to therapy that is backed with a high level of evidence from randomized trial data; category 2A is assigned to treatments backed by less stringent evidence but uniformly approved of by committee members; 2B is assigned to therapies with even less supporting evidence and/or a lack of uniform approval by committee members; and category 3 is assigned to therapies that are regarded with significant disagreement among committee members. It is important to keep in mind that NCCN believes that the best place for any patient is in a clinical trial.

Transplantation

Most clinicians agree that the initial approach to treatment begins with determining whether a patient is a transplant candidate. All treatment algorithms recommended by the NCCN also begin with this approach (NCCN 2008). This initial decision is important because patients who are transplantation candidates must be given an induction therapy that spares stem cells.

Autologous stem cell transplantation (ASCT) following high-dose chemotherapy was introduced as a treatment regimen for myeloma more than 20 years ago. For decades prior to its introduction, patients with myeloma primarily were treated with lower doses of conventional chemotherapeutic agents, such as melphalan (Alkeran) and prednisolone; transplantation — often bone marrow cells rather than the peripheral blood stem cells used today — was generally reserved for salvage or rescue therapy. Standard doses of chemotherapeutic agents alone yielded moderate responses without real survival benefits. However, an intensification of chemotherapy by way of high-dose melphalan, followed by transplantation to restore blood cell production, produced both higher rates of response and the first meaningful survival benefits for patients with myeloma (Attal 1996, Child 2003).

Subsequent randomized trials confirmed the superiority of ASCT in terms of response, despite conflicting results with regard to survival (Bladé 2005; Femand 1998). Until recently, ASCT has been considered a standard treatment for newly diagnosed patients younger than 65 in generally good health, with a transplant-related mortality rate of 1 to 2 percent in this population (Attal 2007). However, ongoing debates exist over the procedure's ability to prolong disease-free survival (DFS) and overall survival (OS) in all patients. Clinical trials that showed a survival benefit with transplantation largely were conducted before the introduction of modern agents, and recent success with novel agents in the frontline setting has led to the prediction that transplantation may eventually become an outmoded procedure. For now, however, all patients in good general health, including many over the age of 65, should be considered possible candidates for ASCT.

Other key issues surrounding transplantation include the timing of the procedure, as some patients benefit from early ASCT and others from delay of the procedure; single versus tandem ASCT, with some patients showing a significant benefit from a second transplant; and the role of allogeneic and mini allogeneic transplantation, both of which involve donor stem cells and have shown promising results (Lee 2003, Kroger 2002, Maloney 2003).

Induction therapy, transplant candidates

No consensus exists with regard to upfront treatment for transplant candidates, as long as the induction therapy does not inhibit subsequent collection of peripheral blood stem cells. Melphalan is no longer used for transplant candidates because it is known to inhibit stem cell collection. High-dose dexamethasone, a synthetic corticosteroid, has been used previously as standard therapy in this setting alone and in combination with other drugs; increasingly, however, there are reports of drawbacks to its use, including serious side effects when combined with modern agents like lenalidomide (Rajkumar 2006b).

Thalidomide (Thalomid), first introduced as a sedative in 1952 and subsequently withdrawn because of highly publicized teratogenicity, has since been proven to have immunomodulatory activity that is useful for the treatment of a number of autoimmune diseases and cancers. In the beginning of this decade, thalidomide was shown to induce apoptosis in myeloma cells resistant to dexamethasone alone, and also was proven to interact synergistically with dexamethasone to potentiate thalidomide's activity (Hideshima 2000, Mitsiades 2002).

After success with thalidomide in the relapse setting, frontline testing began. A number of trials, including a recently published multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone alone as initial therapy for newly diagnosed multiple myeloma, have shown that the combination results both in significantly higher response rates and prolonged time to progression (TTP) (Rajkumar 2008). The addition of thalidomide also does not prohibit stem cell collection. Thalidomide/dexamethasone is a standard treatment for many transplant candidates, and has been approved in the frontline setting for newly diagnosed patients. This combination is associated, however, with a number of adverse effects, including deep vein thrombosis (DVT) and peripheral neuropathy (Rajkumar 2008).

Several trials are evaluating the use of lenalidomide (Revlimid) as a frontline treatment in patients with myeloma. Lenalidomide, an analogue of thalidomide, was developed with the goal of improving the clinical efficacy and safety profiles of its precursor. It is currently FDA approved in combination with dexamethasone for

TABLE

Response rates* with MP, MPT, and MEL100/ASCT in newly diagnosed elderly MM patients

	% of patients (at 12 months)			
Response category	**MP (n=196)**	**MPT (n=125)**	**MEL 100 (n=126)**	***P* value**
Complete response	2	16	17	<.0001
≥90%	8	50	43	<.0001
≥50%	40	81	73	<.0001

*At final analysis, median follow-up time was 37 months.

MEL100/ASCT=reduced intensity stem-cell transplantation after melphalan 100 mg/m^2, MM=multiple myeloma, MP=melphalan and prednisolone, MPT=melphalan and prednisolone with thalidomide.

Source: Facon 2007

use only in patients who have received and failed one prior therapy; however, as with thalidomide, its significant success in relapsed patients led to its clinical testing in those who are newly diagnosed. It has been shown that using a lower dose of dexamethasone when given with lenalidomide in newly diagnosed patients not only reduces side effects, but also improves survival (Rajkumar 2007). Unprecedented response rates of greater than 90 percent have been seen with lenalidomide and dexamethasone in this group of patients, with relatively low rates of toxicity (Rajkumar 2005, Lacy 2006). In general, lenalidomide is better tolerated than thalidomide, with significantly lower rates of neuropathy. Although lenalidomide is associated with an increased risk of myelosuppression and thromboembolic events, particularly DVT, these adverse events generally have proven to be manageable, especially with lower doses of dexamethasone (Zonder 2006, Shah 2007).

Bortezomib (Velcade), a proteasome inhibitor with proapoptotic and antiangiogenic activity, is another novel agent that has undergone significant testing in the relapsed and frontline settings. Bortezomib was recently FDA approved as first-line therapy in the treatment of patients with multiple myeloma. Bortezomib-based therapies have shown consistently high response rates compared with conventional therapies when used as induction regimens for patients undergoing transplantation. In a single-center study of 38 patients, bortezomib in combination with thalidomide and dexamethasone resulted in a response rate of 92 percent and a CR of 18 percent (Wang 2005). Study responses were achieved rapidly and reduced the amount of therapy needed prior to ASCT. Bortezomib also has shown promise in conjunction with doxorubicin and dexamethasone prior to ASCT (Oakervee 2005).

A reported drawback of bortezomib is peripheral neuropathy that can require treatment discontinuation (bortezomib 2008). Bortezomib is unavailable in oral form.

Induction therapy, nontransplant candidates

Until recently, the combination of melphalan and prednisone (MP) has been the standard treatment for elderly patients or for those patients who are otherwise ineligible for transplantation. This combination is now used much less often because of newer, more effective, and less toxic agents that can be used alone or in combination with melphalan or other agents. Recent research has shown that the addition of thalidomide to standard treatment with MP (MPT) may improve response rates, including CR, and may extend progression-free survival (PFS) and overall survival (OS) in newly diagnosed elderly patients (Table).

In a study known as MEL100, 447 newly diagnosed myeloma patients between the ages of 65 and 75 were randomized to 1 of 3 treatment groups. The first received treatment with standard MP, the second with MPT, and the third with two sequential reduced-intensity stem-cell transplantations after melphalan 100 mg/m^2 (Facon 2007). Looking at the primary endpoint, OS, at a median follow-up of 51.5 months, patients on the MPT regimen fared better than those in the two other treatment groups. Patients receiving MEL100 and MP had similar rates of OS. Median OS for patients receiving MPT was 51.6 months, compared with 33.2 months for those receiving MP and 38.3 months for the MEL100 group. PFS and response also were better among patients receiving MPT.

Toxic effects were more common with MPT than with the MP, but were lower than those noted with MEL100. The higher incidence in the MPT group, however, appeared to be counterbalanced by a low incidence of toxicity and early deaths (Facon 2007).

Maintenance therapy

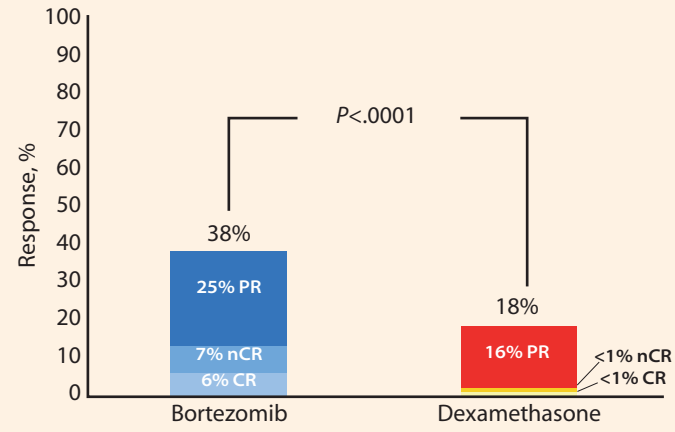
All patients with myeloma, even those who achieve a CR or very good partial response (VGPR) during induction, eventually relapse. The goal of maintenance

therapy is to extend a patient's response to treatment for as long as possible. The most important question with regard to maintenance therapy is whether continued use of a novel agent previously used for induction is appropriate or whether this may result in more resistant relapses.

Growing consensus exists that thalidomide may be the most appropriate agent for use in the maintenance setting. However, one study found that a longer event-free survival (EFS) during the maintenance stage did not necessarily result in longer OS, as compared with other agents (Barlogie 2006).

One randomized trial did demonstrate that thalidomide is an effective maintenance therapy in patients with myeloma (Attal 2006). The study compared no maintenance therapy (arm A), maintenance therapy with pamidronate (Aredia) (arm B), and maintenance with pamidronate/thalidomide (arm C) in patients younger than age 65 (N=597) who were given high-dose induction therapy in the form of a double ASCT two months earlier. Given as adjunctive therapy, pamidronate is a second-generation bisphosphonate, and a potent inhibitor of bone resorption. Although little benefit was seen among patients who received pamidronate alone, improved EFS and OS rates were seen with the addition of thalidomide. Fifty-five percent of patients in arm A, 57 percent in arm B, and 67 percent in arm C achieved CR or VGPR. The 4-year probability of survival was 77 percent in arm A, 74 percent in arm B, and 87 percent in arm C. Once investigators determined that maintenance with thalidomide was superior, the majority of patients crossed over to the thalidomide arm and an overall survival benefit was maintained for those who received thalidomide maintenance therapy upfront. It also was noted that maintenance treatment with pamidronate did not decrease the incidence of bone events. Ongoing clinical trials also are evaluating lenalidomide and bortezomib in this setting.

FIGURE 1
APEX response rates*



*Median follow-up was 8.3 months.
CR=complete response, nCR=near complete response, PR=partial response.
Source: Richardson 2005

Relapsed or refractory myeloma

Several trials provide evidence for agents that may be beneficial for patients whose myeloma has relapsed or become refractory despite prior therapies or transplants.

APEX. In this trial, 669 patients who had received 1 to 3 prior therapies were randomly assigned to receive either:

- Intravenous bortezomib (1.3 mg/m^2 of body-surface area) on days 1, 4, 8, and 11, for eight 3-week cycles, followed by treatment on days 1, 8, 15, and 22, for three 5-week cycles, or
- High-dose dexamethasone (40 mg orally) on days 1 through 4, 9 through 12, and 17 through 20 for four 5-week cycles, followed by treatment on days 1 through 4, for five 4-week cycles.

Compared with patients who received dexamethasone, patients who received bortezomib had higher response rates, significantly longer TTP (6.2 versus 3.5 months), and longer survival rates (Figure 1).

The 1-year survival rate was 80 percent among patients taking bortezomib and 66 percent among patients taking dexamethasone (P=.003) (Richardson 2005). Because of the beneficial results with bortezomib, patients who were assigned to receive dexamethasone were permitted to cross over to receive bortezomib in a companion study.

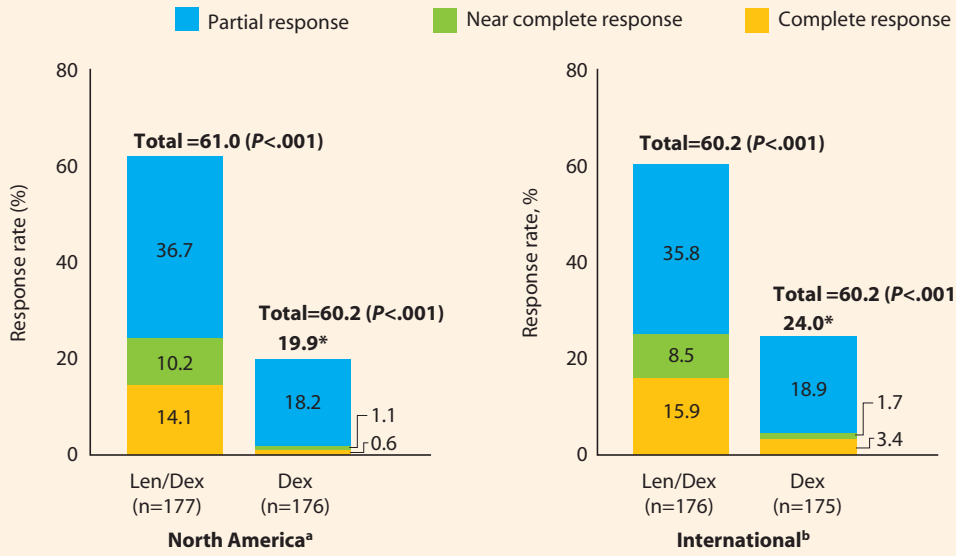
Significant primary toxicities associated with the use of bortezomib during the trial included thrombocytopenia and peripheral neuropathy. A small number of patients developed severe neuropathy (approximately 9 percent), which was expected to be permanent in about half of this subgroup.

Lenalidomide trials. Two large phase 3 trials — one based in North America (Weber 2007) and an international study (Dimopoulos 2007) demonstrated significantly superior TTP in addition to exceptional overall response rates and unprecedented rates of survival with lenalidomide plus dexamethasone, when compared with placebo plus dexamethasone (Figure 2, page 14).

All patients — the majority of whom had relapsed after multiple prior therapies and transplantation —were randomized to receive lenalidomide 25 mg (days 1 through 21) with pulsed dexamethasone, or dexamethasone alone. The overall response rates among patients

FIGURE 2

Phase 3 trials of lenalidomide/dexamethasone in relapsed or refractory multiple myeloma



Dex=dexamethasone, Len=lenalidomide.
Sources: [a]Weber 2007, [b]Dimopoulos 2007

who received lenalidomide were exceptionally high (61 percent in the North American trial and 59 percent in the international trial). CR rates also were higher among patients who received lenalidomide with dexamethasone.

Perhaps the most remarkable difference between the two treatment groups was with regard to TTP; the combination of lenalidomide and dexamethasone significantly extended the median TTP, from 4.7 months to 11.1 months in the North American study ($P<.001$), and from 4.7 months to 11.3 months in the international study ($P<.001$). This was the longest TTP observed to date in a phase 3 trial with previously treated patients.

Although use of lenalidomide results in far less neuropathy than seen with thalidomide, greater myelosuppression occurs. In these two trials, patients had a high degree of grade 3/4 neutropenia (nearly 40 percent), but a low incidence of febrile neutropenia (less than 3 percent in both trials). Other adverse events reported with the combination of lenalidomide and dexamethasone were muscle cramps, constipation, nausea, tremor, and dizziness. These effects were manageable with dose adjustments.

Another significant finding in these two trials was a remarkably high activity level in patients who had previously received thalidomide compared with those who had not (53 percent versus 63 percent). This response, even in patients previously exposed to the analogue of lenalidomide, was much higher than expected. This finding has created an interest in determining whether patients who fail treatment with lenalidomide will respond to thalidomide, and adds to the growing emphasis on determining the proper sequencing of agents in all treatment regimens. Clinical trials examining this issue are ongoing.

Conclusion

Although myeloma remains incurable, management of the disease has significantly improved with the introduction of novel agents. As various regimens continue to undergo testing, a major focus of ongoing trials will be determining the optimal combination and sequencing of novel and conventional therapies. In addition, insights into the role of the tumor microenvironment are expected to continue to generate newer targeted approaches.

Considerable variations in the clinical manifestations of myeloma and in the patient response to treatment, together with the availability of an increasing number of treatment options, have led clinicians to adopt a more personalized approach to care. Decisions regarding treatment should begin with a long-term plan that incorporates both a patient's prognosis and their QoL goals.

References

American Cancer Society. Cancer Facts and Figures 2008. «http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf.» Accessed June 3, 2008.

Attal M, Harousseau JL. Role of autologous stem-cell transplanta-

tion in multiple myeloma. *Best Pract Res Clin Haemotol.* 2007;20:747–759.
Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood.* 2006;108:3289–3294.
Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroup Francais du Myelome. *N Engl J Med.* 1996;335:91–97.
Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoetic-cell transplantation for multiple myeloma. *N Engl J Med.* 2006;354:1021–1030.
Bladé J, Rosiñol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood.* 2005;106:3755–3759.
Bortezomib (Velcade) [prescribing information]. June 2008. «http://www.velcade.com/full_prescrib_velcade.pdf». Accessed June 24, 2008.
Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348:1875–1883.
Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007;357:2123–2132.
Durie BGM. *Multiple Myeloma: Cancer of the Bone Marrow. Concise Review of Treatment Options and Patient Handbook.* N. Hollywood, Calif.: International Myeloma Foundation. 2007.
Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet.* 2007;370:1209–1218.
Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up front or rescue treatment? Results of a multicenter sequential randomized trial. *Blood.* 1998; 92:3131–3136.
Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood.* 2000;96:2943–2950.
Kröger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood.* 2002;100:755–760.
Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003;78:21–33.
Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med.* 2007;356:2582–2590.
Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002;346:564–569.
Lacy M, Gertz M, Dispenzieri A, et al. Lenalidomide plus dexamethasone (Rev/Dex) in newly diagnosed myeloma: response to therapy, time to progression, and survival. ASH Annual Meeting Abstracts. *Blood.* 2006;108:798.
Lee CK, Badros A, Barlogie B, et al. Prognostic factors in allogeneic transplantation for patients with high-risk multiple myeloma after reduced intensity conditioning. *Exp Hematol.* 2003;31:73–80.
Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood.* 2003;102:3447–3454.
Mitsiades CS, Mitsiades NS, Richardson PG, et al. Multiple myeloma: a prototypic disease model for the characterization and therapeutic targeting of interactions between tumor cells and their local microenvironment. *J Cell Biochem.* 2007;101:950–968.
Mitsiades N, Mitsiades CS, Poulaki V, et al. Apoptotic signaling induced by immunomodulatory analogs in human multiple myeloma cells: therapeutic implications. *Blood.* 2002; 99:4525–4530.
NCCN (National Comprehensive Cancer Network). NCCN Practice guidelines in Oncology: Multiple Myeloma-V.1.2008. «http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf». Accessed June 24, 2008.
Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin, and dexamethasone) for previously untreated patients with multiple myeloma. *Br J Haematol.* 2005;129:755–762.
Rajkumar SV, Dispenzieri A, Kyle RA. Monoclonal gammopathy of undetermined significance, Waldenström macroglobulinemia, AL amyloidosis, and related plasma cell disorders: diagnosis and treatment. *Mayo Clin Proc.* 2006a;81:693–703.
Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed multiple myeloma. *Blood.* 2005;106: 4050–4053.
Rajkumar SV, Jacobus S, Callender N, et al. A randomized phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4Ao3): a trial coordinated by the Eastern Cooperative Oncology Group. ASH meeting abstract. Blood. 2006b;108:111:799.
Rajkumar SV, Jacobus S, Callender N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4Ao3): a trial coordinated by the Eastern Cooperative Oncology Group. ASCO meeting abstract. *J Clin Oncol.* 2007;25(185):LBA8025.
Rajkumar SV, Rosiñol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol.* 2008;26:2171–2177.
Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2005;352:2487–2498.
Ries LAG, Melbert D, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975–2004. SEER Cancer Statistics Review 1975–2004. National Cancer Institute. «http://seer.cancer.gov/csr/1975_2004/results_merged/sect_18_myeloma.pdf.» Accessed June 3, 2008.
Shah SR, Tran TM. Lenalidomide in myelodysplastic syndrome and multiple myeloma. *Drugs.* 2007;67:1869–1881.
Wang M, Delasalle K, Giralt S, et al. Rapid control of previously untreated multiple myeloma with bortez-thal-dex followed by early intensive therapy. *Blood.* 2005;106:231.
Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;357:2133–2142.
Zonder JA, Barlogie B, Durie BGM, et al. Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis. *Blood.* 2006;108:403–404.

Disclosures: Joseph M. Tuscano, MD, has received honoraria from Amgen, Celgene, and Genentech. He reports no real or apparent conflicts of interest with respect to proprietary products mentioned in this article.

Balancing the Policy With Appropriate Patient Care

RICHARD G. STEFANACCI, DO, MGH, MBA, AGSF, CMD
Executive Director, Center for Medicare Medication Management
University of the Sciences in Philadelphia, Mayes College of Healthcare Business and Policy

SUMMARY

Major changes are underway at CMS that may affect practices among health plans and providers. If implemented, these changes could alter the delivery of cancer care.

All of the Centers for Medicare & Medicaid Services silos affect the care of cancer patients. Medicare Part A covers transfusions, transplants, and surgeries performed at hospitals. Part B covers care provided by physicians, including the administration of injectable medications. Part D covers outpatient prescription drugs, while Part C, the Advantage Plan, includes all of these components provided through managed care plans.

Major changes are underway at CMS that may affect how health plans and providers design their practices for 2010, and more specifically, how they will care for their cancer patients.

RICHARD G. STEFANACCI, DO, MGH, MBA, AGSF, CMD

Medicare Part A

Changes to Part A focus on inpatient drug coverage and pay-for-performance issues.

Inpatient drug coverage. Coverage of subacute care stays in nursing homes falls under Part A. The facility is financially responsible for the medications that are given during the subacute stay. This stay lasts for as long as the patient's subacute needs remain, or 100 days, whichever occurs first. The Office of the Inspector General will now investigate nursing facilities suspected of shifting their financial responsibility to other payers.

An example of such an action might pertain to patients who take oral cancer agents. If a facility informs a patient's family that, "We can't get that medication. It's easier for you to take these prescriptions and fill them at the pharmacy and bring them back to us," that facility thereby shifts responsibility for payment from Part A to Part D, so that the health plans must make payment. Health plans should be aware of the Part A to D shift. Verifying whether patients are subacute Part A nursing home residents (if so, they are already covered) can accomplish this task.

To a lesser extent, facilities also are shifting responsibility to Part B. A facility may instruct the family to take a patient to a physician's office to have a drug infused, for example, rather than having it administered on site. However, this is a gray area, as clinical reasons may exist for making the shift. The keys here lie in knowing both the site and level of care that is being provided so that payer determination can easily be made.

Pay for performance. The high level of hospital readmissions that occurs within a 30-day time frame is of concern to CMS. Going forward, its proposal is to hold back 5 percent of its payment to hospitals until it has been assured that a patient will not be readmitted for the original diagnosis or for a complication of that diagnosis. If either of these actions takes place, the hospital will be penalized. Due to high readmittance levels among oncology patients, hospitals that care for this patient population will certainly be affected.

The goal of the proposal is to improve "transitions of care," or discharge planning. CMS wants to make sure that patients who go home with heavy regimens of medications — as cancer patients do — understand why they

---

Richard G. Stefanacci, DO, MGH, MBA, AGSF, CMD, is the founding executive director of the Health Policy Institute at the University of the Sciences in Philadelphia. He completed his clinical training in Internal Medicine at the University of Medicine and Dentistry of New Jersey and obtained a fellowship in geriatrics. His geriatric experience includes more than a decade in several medical director positions, and he has achieved recognition as a fellow in the American Geriatrics Society (AGSF). In addition to writing and lecturing extensively, he serves as editor in chief of the Assisted Living Consult, and serves on the editorial boards of Caring for the Ages, *Thomas Jefferson University's Health Policy newsletter, and the* Journal of Quality Healthcare.

are taking these drugs and have access to them even before they leave the hospital.

In addition to focusing on readmissions, CMS is looking at hospital-acquired conditions. Beginning Oct. 1, 2008, CMS will no longer pay hospitals to treat conditions that were not diagnosed as present on admission (POA) to the hospital. There are eight conditions that hospitals must begin to document as POA, all of which could apply to a cancer patient (Table 1).

With this new policy in place, hospitals must be more attentive to preventing these conditions, or take care to diagnosis them when present at the time of admission. From the perspective of CMS, hospitals should take preventive measures to ensure that such injuries as pressure sores and falls in the hospital do not occur during an admission.

Changes to Medicare Part B

Vaccine coverage has been altered, and the Physician Quality Reporting Initiative (PQRI) will undergo changes. Part B also is examining access issues, influences on key stakeholders, and cost-control methods.

Vaccines. Three vaccines plus one are covered by Part B: influenza, pneumococcal, and hepatitis B. The plus one is the tetanus vaccine that is covered by Part B if it is given as a result of an acute injury, and by Part D if a patient received it as part of a preventive booster because it has been 10 years or more since the patient's last shot.

CMS requires that all other vaccines be covered under Part D. With the present changes, Part D not only covers the vaccines, but their administration as well. For example, physicians who provided patients with vaccines in December 2007 would have billed Part B; now they must bill patients, who, in turn, must submit a claim to Part D for reimbursement (unless a system has been worked out between the physician and the plan for direct billing).

An area of concern — especially within the oncology, geriatrics, and Alzheimer's disease fields — is that patients might have difficulty getting access through Part D to the increasing number of new vaccines. It is feasible for patients to fall into coverage gap commonly referred to as "the doughnut hole" and be left to pay 100 percent of the cost of both the vaccine itself and its administration. As such, physicians are administering fewer vaccines in their offices as pharmacists are gaining approval to do so in more and more states. This trend is expected to persist.

PQRI. Addressing every medical specialty, the PQRI is the major pay-for-performance effort within physicians' services. When this voluntary program began in July 2007, there were 74 measures; there are now more tha 100, many of which are medication-related. The goal of the PQRI is to drive physicians to more appropriate behavior, as CMS remains concerned with physician reimbursement being based purely on the volume of services rendered.

TABLE 1

Present on admission

As of fiscal year 2009, CMS will no longer reimburse for hospital-acquired conditions that are not documented as "present on admission." The conditions:

1. Object left in during surgery
2. Air embolism
3. Blood incompatibility
4. Catheter-associated urinary tract infection
5. Pressure ulcers
6. Vascular catheter-associated infections
7. Surgical site infection — mediastinitis after coronary bypass graft
8. Falls and trauma, including fractures, dislocations, intracranial injuries, crushing injuries, and burns

Source: CMS

The following is an example of how PQRI works: an oncologist completes three of the oncology measures at least 80 percent of the time for their Medicare patients who require that measure. As a result, the practitioner is eligible to receive an additional 1.5 percent reimbursement of their total Part B reimbursement for direct physician services. This extra payment could be a significant amount in certain specialties, including oncology.

Data pertaining to PQRI is beginning to be analyzed by CMS and reported to the participating physicians. Because it is a rather complex system, participation was poor — 15 percent — in the program's first 6 months (CMS 2008). Program utilization was greatest among emergency room, ophthalmology, and radiology physician groups, probably in part due to the fact that much of the required data for these speciality areas were already being captured.

A similar trend was seen with hospital participation in their pay-for-performance programs. These programs also started with low initial participation rates, which have since increased to the current rate of over 90 percent (CMS 2008). The same increase will most likely be seen in PQRI participation as the dollar amounts involved increase. Although PQRI will always be considered a voluntary program, the financial gains will be an effective incentive to gain significant participation.

Defining access. The U.S. Food and Drug Administration and CMS both are working to ensure that the right drugs are being given to the right patients in appropriate doses and durations by defining access standards. The increased use of risk maps restricts access to medications to only those appropriate patients and guarantees that only appropriate physician groups are able to prescribe certain medications. Many risk maps require physicians to be certified and to sign consent forms, as well as have authorization from the patient. Risk mapping is particularly important in oncology. As more and more medications with

narrow therapeutic windows and high toxicity profiles become available, the FDA and CMS are expected to push for more extensive use of risk maps.

Other areas being explored include specific diagnostic testing, including tumor marking. CMS is looking into how to align incentives to encourage the use of this tool. The FDA is narrowing labeling indications, as was seen in the recent case of erythropoietin products. Both agencies also are looking at clinical practice guidelines and are considering using some guidelines that go beyond compendium recommendations, especially in the area of oncology.

Influencing key stakeholders. CMS wants to ensure that such areas as direct-to-consumer (DTC) advertising and detailing do not improperly influence prescribers and patients. However, there are some benefits that are derived from these practices. For example, a caregiver may gain increased awareness through DTC of a loved one's physical changes or mental decline, and bring that patient into the physician's office for evaluation. Without the knowledge obtained from DTC advertising, some patients would go without treatment, as they may be unaware of the need to do so on their own.

Cost controls. One of the ways CMS is trying to rein in costs is through the use of least costly alternatives (LCAs). In these instances, CMS may seek to show a class effect, espousing that all of the agents within this drug class are equivalent, and are therefore subject to therapeutic interchange. No matter how much CMS is charged for these products, it will pay only the cost of the LCA. More use of this approach is expected in the future.

Changes to Medicare Part D

CMS will continue to evaluate Part D, especially in the areas of the protected drug classes and excluded medications, the doughnut hole, and Formulary Key Drug Type (FKDT), as well as in regard to premium problems and Medication Therapy Management (MTM).

Protected classes and excluded medications. Six protected classes currently exist: oncology agents, atypical antipsychotics, antidepressants, anticonvulsants, immunosuppressants, and HIV/AIDS drugs. CMS has been considering the elimination of two of these protective classes — atypical antipsychotics and antidepressants. Several of the potentially excluded drugs are important to cancer patients. Legislation has been pending since 2005 to maintain the inclusions of benzodiazepines. The cost of such an amendment would likely be low, and might actually be cost-neutral or result in limited cost savings (Medical Rights Center 2005). The eventual outcome is still unclear. Conversely, HIV/AIDS drugs and cancer drugs are unlikely to be eliminated, so plans will continue to be responsible for including almost all of their medications on their formularies.

The doughnut hole and risk corridors. The doughnut hole is a major issue for cancer patients, as the vast majority of them fall into this ever-expanding chasm. The catastrophic threshold was $5,100 in 2006; today, it's almost $6,000 (Table 2). As CMS tries to move more coverage from Part B to Part D, shifting obligation and control to the plans, the effect of the doughnut hole increases, especially in oncology.

When patients hit the catastrophic threshold, they are responsible for 5 percent of the cost of medication, the health plan for 15 percent, and the federal government for 80 percent. CMS is likely to push legislation to drop this system when it sunsets, but it will continue the risk corridors. Risk corridors and reinsurance for plans will sunset over the next 2 years, and will likely have a major impact on how plans manage cancer patients.

FKDT. After health plans made their submissions last year, CMS eliminated the requirement that plans must offer one drug in each FKDT. As plans submit their data to CMS, it is apparent that the relaxed formulary requirement is being applied at an increasing rate. The elimination of the need to provide formulary coverage

TABLE 2

The ever-growing doughnut hole

Year	Average beneficiary premium	Deductible	Initial benefit limit	Catastrophic threshold	Out-of-pocket spending at threshold*
2006	$23.00	$250	$2,250	$5,100.00	$3,600
2007	$35.86	$265	$2,400	$5,451.25	$3,850
2008	$37.19	$285	$2,580	$5,871.25	$4,150
2009	$39.64	$310	$2,770	$6,295.00	$4,450
2010	$42.39	$330	$2,980	$6,737.50	$4,750
2011	$45.36	$355	$3,200	$7,233.75	$5,100
2012	$48.52	$380	$3,440	$7,795.00	$5,500

*Out-of-pocket spending at threshold does not include amounts paid in monthly premiums.

Source: National Committee to Preserve Social Security and Medicare, 2006.

of a least one FKDT will have the greatest impact on Parkinson's disease agents, diabetes drugs, cardiovascular medications, and antibacterial agents. Because cancer drugs are protected, they are unaffected by this change in formulary requirements.

For now, no major changes are expected related to formulary requirements, but when a new administration takes over after the November elections, substantial changes will certainly be in store for 2010 and beyond.

The premium problem. CMS is concerned about the effect of substantial plan premium increases as they relate to the dually eligible (those who are eligible for both Medicare and Medicaid), a significant number of whom became ineligible for plans after premiums were raised. Even if a plan's premium is higher than the regional benchmark, CMS still subsidizes at the benchmark level. If dual eligibles want to stay in a plan whose premium is above the regional benchmark, they would have to pay the difference. CMS has looked at this situation — which is particularly disruptive to the older, frail patient population — and will encourage plans not to shift their obligation for the dually eligible to other plans.

MTM. When CMS drafted MTM regulations, its objective was to ensure that plans were provided to "targeted beneficiaries," or those who take multiple prescriptions, suffer from several chronic illnesses, and incur over $4,000 per year in expenses. Plans can define how many and which types of medications fall within this regulation, as well as the number and type of chronic illnesses required to be an eligible participant in MTM services (AMCP 2008).

Given the complexity and expense of oncology treatments, cancer patients typically qualify for MTM. Between 5 and 15 percent of most plans' members fall into the MTM category. When MTM is an opt-in program, participation ranges from an abysmal 3 to 10 percent. As an opt-out program, participation rates rise substantially. In an opt-out program, plan members typically receive a letter telling them they are in MTM and will be contacted by pharmacy staff unless they sign a document declaring that they are opting out.

Not surprisingly, patients who qualify for MTM tend to be the highest utilizers. They are the people who fall into the doughnut hole. CMS is seeking to change some of the definitions of MTM. Right now, any qualified provider can provide MTM, but in the future, pharmacists will provide MTM. More aggressive and diligent use of MTM by pharmacists, especially with cancer drugs, is expected.

CMS is looking for specific measures that will hold plans accountable for MTM. These measures will likely come from the work that the Pharmacy Quality Alliance is doing, which now applies only to retail and long-term care pharmacy, but could later be applied to plans for their MTM programs.

Changes to Medicare Part C: SNPs

There has been a significant increase in special needs plans (SNPs), and many cancer patients qualify for them. SNPs cover unique groups, including institutionalized seniors or those living in nursing homes; the dually eligible, which is the largest SNP group covered; and those with chronic illnesses.

As cancer increasingly becomes a chronic illness, SNPs will be developed for cancer patients. These programs have demonstrated improved outcomes through an integrated interdisciplinary team that manage these patients, covering all of their Parts A, B, and D benefits. Greater use of this strategy is expected in the future. There presently exists a moratorium on SNPs because of congressional worry regarding their rapid growth, but this will likely be lifted by year's end.

Conclusion

Pay-for-performance efforts for hospitals, PQRI for physicians, and defining access through the use of risk maps, diagnostic testing, labeling, and guidelines are all strategies for improving outcomes and making sure that the right medications are being given to the right patients. CMS will hold plans accountable for MTM, and it will discourage plans from shifting the responsibility for dual eligibles to other plans through increased premiums. These strategies will affect not only cancer patients, but also the providers and plans involved in their care.

References

AMCP (Academy of Managed Care Pharmacy). Sound medication therapy management programs described by health care and business leaders. April 6, 2008. «http://www.amcp.org/amcp.ark?c=news&type=pr&id=454.» Accessed June 11, 2008.

CMS. Proposed changes to the hospital inpatient prospective payment systems and fiscal year 2009. April 14, 2008. «http://www.medicalnewsservice.com/fullstory.cfm?storyID=4929&fback=yes.» Accessed June 11, 2008.

Medicare Rights Center. Critical coverage: benzodiazepines under Medicare Part D. June 2005. «http://www.medicarerights.org/benzoreport.pdf.» Accessed June 11, 2008.

National Committee to Preserve Social Security and Medicare. Viewpoint: Medicare's doughnut hole: a bitter pill to swallow. «http://www.ncpssm.org/news/archive/vp_donuthole.» Accessed June 26, 2008.

Disclosure: Richard G. Stefanacci, DO, MGH, MBA, AGSF, CMD, reports having received grant and research support from the American Society of Consultant Pharmacists, sanofi-aventis, Amgen, and Merck, and consulting fees from Celgene, NewCourtland Elder Services, Baxter Healthcare, Eisai, Pfizer, sanofi-aventis, Sepracor, Amgen, Merck, and Johnson & Johnson. He also serves on the speaker's bureau for Pfizer, Ortho McNeil, Abbott, GlaxoSmithKline, AstraZeneca, Forest Laboratories, Amgen, Merck, Daiichi Sankyo, Par, Eisai, and Schering-Plough, and the advisory boards for Pfizer, Eisai, Janssen, Solvay, Takeda, and Genentech. He reports having been compensated for work related to darbepoetin alfa (Aranesp).

CONTINUING MEDICAL EDUCATION ASSESSMENT/EVALUATION/CERTIFICATE REQUEST

Hematologic Cancer as a Chronic Disease

CE Credit for Physicians/Pharmacists

I certify that I have completed this educational activity and post-test and claim *(please check one)*:
☐ Physician credit hours
☐ Pharmacist contact hours

Signature: _____

PLEASE PRINT CLEARLY

First name, MI _____

Last name, degree _____

Title _____

Affiliation _____

Mailing address _____

_____

City_____ State ___ ZIP_____

Daytime telephone (____) _____

Fax (_____) _____

E-mail _____

Physicians — This activity is designated for a maximum of 2.0 *AMA PRA Category 1 Credits.*™

Pharmacist — This activity is approved for 2.00 contact hours (0.2 CEU).

ACPE Universal Program Number (UPN): 812-000-08-017-H01-P
Release Date: July 15, 2008
Expiration Date: July 15, 2009

To receive a statement of credit, complete the assessment/evaluation form and mail or fax the completed form to:

The Chatham Institute
26 Main Street, Suite 350
Chatham, NJ 07928
Fax: (973) 701-2515

Allow 6–8 weeks for processing.

This activity is sponsored by The Chatham Institute and is provided at no cost to the participant through an educational grant from Celgene Corp.

T7Q58-MG

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on page 21. There is only ONE correct answer per question. Place all answers on this form.

	A.	B.	C.	D.
1.	☐	☐	☐	☐
2.	☐	☐	☐	☐
3.	☐	☐	☐	☐
4.	☐	☐	☐	☐
5.	☐	☐	☐	☐
6.	☐	☐	☐	☐
7.	☐	☐	☐	☐
8.	☐	☐	☐	☐
9.	☐	☐	☐	☐
10.	☐	☐	☐	☐

PROGRAM EVALUATION

So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the objectives for the activity been met?

1. Review clinical advances, including current and emerging therapeutics, and the epidemiology of hematologic cancers, specifically multiple myeloma and myelodysplastic syndromes.
☐ Yes ☐ No

2. Discuss the components of the Medicare policy in the area of oncology.
☐ Yes ☐ No

3. Assess best practices for cancer management within a managed care setting and the impact of the managed care pharmacist on patient care.
☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias?
☐ Yes ☐ No

If no, please explain: _____

_____

_____

_____

Please use the following scale to answer the next four questions:

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

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Treat/manage patients?
5 4 3 2 1 N/A

Communicate with patients?
5 4 3 2 1 N/A

Manage my medical practice?
5 4 3 2 1 N/A

Other _____

_____
5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	*Very good*	*Good*	*Fair*	*Poor*
5	4	3	2	1

What other topics would you like to see addressed? _____

_____

_____

_____

Comments: _____

_____

_____

_____

CONTINUING EDUCATION POST-TEST

Hematologic Cancer as a Chronic Disease

Please tear out the assessment/evaluation form on page 20. On the answer sheet, place an X through the box of the letter corresponding to the correct response for each question. There is only ONE correct answer to each question.

1. **The two most significant risk factors for myelodysplastic syndromes (MDS) are:**
   a. Age and smoking.
   b. Fanconi's anemia and prior drug use.
   c. Radiation exposure and smoking.
   d. Prior treatment of cancer and a patient's age.

2. **Which of the following is NOT a pathophysiological feature of MDS:**
   a. Hematopoietic stem cells' failure to differentiate properly.
   b. Bone marrow populated with dysplastic cells.
   c. An increase in apoptosis that occurs among healthy cells in the bone marrow.
   d. Hematopoietic stem cells dramatically decrease in number.

3. **The most common cytopenia found among patients with MDS is:**
   a. Neutropenia.
   b. Thrombocytopenia.
   c. Anemia.
   d. Leukocytopenia.

4. **Treatment with erythropoietin (EPO) is most effective in patients whose serum EPO level is:**
   a. Below 500 mU/mL.
   b. Between 450 and 550 mU/mL.
   c. Above 500 mU/mL.
   d. Between 475 and 575 mU/mL.

5. **Lytic bone lesions occur in which percentage of patients with myeloma?**
   a. 20.
   b. 80.
   c. 70.
   d. 40.

6. **According to the National Comprehensive Cancer Network, patients with asymptomatic myeloma do not require treatment, but should be observed every:**
   a. 3 to 6 years.
   b. 9 to 12 months.
   c. 1 to 2 years.
   d. 3 to 6 months.

7. **In 2007, the *New England Journal of Medicine* published two large trials regarding the use of _____ for the treatment of patients with relapsed/refractory myeloma:**
   a. Melphalan.
   b. Thalidomide.
   c. Bortezomib.
   d. Lenalidomide.

8. **According to changes that have occurred in Medicare, which of the following vaccines falls under Part B coverage if it is given as a result of an acute injury to the patient?**
   a. Tetanus.
   b. Influenza.
   c. Pneumococcal.
   d. Hepatitis B.

9. **When examining protected classes of medicine under Medicare Part D, which of the following groups is NOT included?**
   a. HIV/AIDS mediations.
   b. Anticonvulsants.
   c. Immunosuppressants.
   d. Nonsteroidal anti-inflammatory agents.

10. **When a patient hits the catastrophic coverage threshold, what share of the cost of their medications do they become responsible for?**
    a. 1 percent.
    b. 5 percent.
    c. 10 percent.
    d. 15 percent.