**MYELODYSPLASTIC SYNDROMES (MDS)**
New Approaches to Achieve Best Practices in Treating MDS

Managed Care Clinical Oncology Expert Roundtable
Dallas, July 31, 2009

**HIGHLIGHTS**

- Current MDS Landscape
- Emerging Therapies, Survival, and Alternative Outcomes
- Alternative Dosing Schedules for Methylation Inhibitors
- Role of Specialty Pharmacy
- Health Care Management Considerations

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Myelodysplastic Syndromes (MDS): New Approaches to Achieve Best Practices In Treating MDS
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The treatment of myelodysplastic syndromes (MDS) has gained substantial attention in the last few years with the development of novel therapies capable of altering the natural history of the disease. Prior to 2001, there was a limited collection of epidemiologic data, but the addition of these stem cell malignancies to the North American Association of Central Cancer Registries has led to a better understanding of the extent and impact of the disease and a greater interest in therapeutic intervention (Rollison 2008).

A disease predominantly of older adults, with more than 70 percent of diagnoses occurring after age 50, treatment has long consisted of palliative care — many of these patients were considered too old to tolerate the treatments for myeloproliferative disorders, dose-intensive chemotherapy, and bone marrow transplantation (HMDS 2009, Hellström-Lindberg 1999, Silverman 2001). Yet, MDS is a deadly disease, with 36 percent to 50 percent of patients dying of infectious complications or bleeding within 3 to 4 years, and 35 percent to 40 percent progressing to acute myelogenous leukemia (Hoffman 2000, Kantarjian 2002, Kurzrock 2002, Silverman 2001). It has been estimated that 9,700 new cases of MDS are diagnosed each year in the United States, with higher rates occurring among men and among whites and non-Hispanics; the median survival is 2 to 3 years (Rollison 2008). Because of the heterogeneous nature of MDS — it comprises a group of hematologic disorders marked by ineffective hematopoiesis, peripheral blood cytopenias, and bone marrow failure — the disease burden is likely underestimated. Goldberg (2008) performed a retrospective analysis of new primary MDS diagnoses filed in the Medicare Standard Analytical File 5 percent (SAF5%) claims database in 2003 (excluding patients with myeloid leukemia or anemias of known causes in the previous year) and reports quite different numbers (Table). Goldberg estimated an incidence of more than 76,000 adults with MDS rather than the 10,300 anticipated based on Surveillance Epidemiology and End Results data (Rollison 2008). Clearly, this is a condition that calls out for effective treatment.

As a disease of hematopoietic dysfunction, a number of hematologic therapies have been tested with variable benefit. Growth factors are a logical choice to stimulate

### INTRODUCTION

**Myelodysplastic Syndromes (MDS): The Current Landscape**

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**Executive Vice President and Chief Medical Officer**  
**MediMedia USA**

The treatment of myelodysplastic syndromes (MDS) has gained substantial attention in the last few years with the development of novel therapies capable of altering the natural history of the disease. Prior to 2001, there was a limited collection of epidemiologic data, but the addition of these stem cell malignancies to the North American Association of Central Cancer Registries has led to a better understanding of the extent and impact of the disease and a greater interest in therapeutic intervention (Rollison 2008).

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As a disease of hematopoietic dysfunction, a number of hematologic therapies have been tested with variable benefit. Growth factors are a logical choice to stimulate

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**Table**  
**MDS incidence in the Medicare population in 2003 – ICD-9-CM code 238.70**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Medicare data</th>
<th>SEER data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>92</td>
<td>7.4</td>
</tr>
<tr>
<td>60-69</td>
<td>138</td>
<td>16</td>
</tr>
<tr>
<td>70-79</td>
<td>199</td>
<td>34</td>
</tr>
<tr>
<td>&gt;80</td>
<td>261</td>
<td>37</td>
</tr>
</tbody>
</table>

Total: 76,600 10,300

* Bone marrow documentation in 53% of population; higher incidence in men.

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*Rollison 2008  
MDS=myelodysplastic syndromes, SEER=Surveillance Epidemiology and End Results.  
Source: Goldberg 2008
blood cell production, but may simultaneously induce proliferation and survival of preleukemic cells (Gordon 1999). In clinical trials, patients with low serum erythropoietin levels and minimal need for red cell transfusion have been found to benefit from erythropoietin treatment, but other MDS patients respond poorly (Silverman 2001). Neutrophil, platelet, and pleiotropic growth factors have been examined as hematopoietic support, but these approaches have failed to increase survival in MDS and may be associated with substantial treatment-related toxicity (Demetri 2001, Gordon 1999, Silverman 2001). Response rates with standard induction chemotherapy (anthracycline and cytarabine) are impressive, but relapse is rapid, occurring within a median duration of less than 1 year (Silverman 2001) and without an increase in survival.

The hypomethylating agents azacitidine and decitabine have provided new hope for MDS patients. By mitigating methylation of DNA, these agents allow the healthy reproduction of previously quiescent genes. In early clinical trials, they produced promising results, including hematologic improvement, delayed disease progression, and clinical remissions (Cheson 1998, Kizaki 1992, Saba 2005, Silverman 1994, Silverman 2001, Silverman 2002), and with azacitidine, overall survival (Fenaux 2007, Silverman 2002). As a result of these outcomes, patients today are more likely to be identified earlier in the course of the disease, referred to academic centers for novel therapy, and offered multiple treatment options. We also can hope to realize the goals of cancer therapy — delayed progression, prolonged survival, and improved quality of life.

With new treatments come increasing challenges for health care plans and providers. Each advance in the medical management of disease necessitates that new integrative delivery and financing systems be adapted, specialty pharmacies be updated, and clinicians be kept abreast of how a new state-of-the-art medication will alter patient care. These changes also will affect the resources of managed care organizations, making it essential that payers and providers collaborate to develop rational strategies for coverage and reimbursement and redefine protocols to maximize patient outcomes and minimize treatment costs.

The articles in this publication are based on the Managed Care Clinical Oncology Expert Roundtable held in Dallas in July 2009. The authors address current MDS issues and how changing approaches to MDS treatment, and in particular higher-risk MDS, will affect all health care stakeholders — providers, patients, and health plans. They offer potential strategies for merging treatment benefit with the limited resources of health care plans to achieve best practices in treating MDS. Each presentation by an Expert Panel member is followed by a Q&A discussion. Our intent in sharing this dialogue with our readers is to provide a better understanding of MDS and to promote collaboration among health care stakeholders to ensure optimal patient outcomes.

References
Myelodysplastic Syndromes: Emerging Therapies, Survival, and Alternative Outcomes

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KEY POINTS
• Novel therapeutics, such as hypomethylating agents, growth factors, immunotherapeutics, and biologic response modifiers, are improving outcomes in patients with MDS.
• The hypomethylating agents azacitidine and decitabine slow disease progression, and azacitidine has been shown to prolong survival.
• Early diagnosis and classification of MDS is necessary to best utilize the range of therapies now available.
• MCO decision makers should evaluate all available data on agents proven effective in treating MDS to define a treatment protocol.

The myelodysplastic syndromes (MDS) are a group of clonally derived hematologic disorders characterized by morphologic abnormalities of myeloid pluripotent stem cells, ineffective hematopoiesis, and resultant blood dysplasias (Buckner 2008, Rollison 2008). Patients generally are identified via the presence of peripheral cytopenias and their common symptoms — anemia, heart failure, infection, bruising, and hemorrhage. The most frequent presenting feature is anemia, often macrocytic in nature, but abnormalities of neutrophils, monocytes, and platelets also may be observed (Cazzola 2005, HMDS 2009, NCCN 2009). In some patients with specific subtypes, circulating blasts are present (HMDS 2009). The natural history generally progresses from peripheral cytopenia to transfusion dependency, with approximately 30 percent of patients advancing to acute myeloid leukemia (AML) (Disperati 2006, Rollison 2008).

MDS are primarily disorders of the elderly; the median age at diagnosis is approximately 70 years, and 70 percent of patients are age 50 or older (HMDS 2009). The incidence increases with advancing age, and the rate has been shown to be 5 times higher among subjects age 80 or older compared to those age 60 to 69 years (Buckner 2009) and is highest among white and non-Hispanic men (HMDS 2009, Rollison 2008).

Treatment of MDS has improved substantially in the last decade. Whereas patients with MDS were generally treated with a wait-and-see approach and allogeneic stem cell transplantation when needed, now biologic and chemotherapeutic treatments are proving effective in controlling symptoms and preventing disease progression. Novel therapeutics such as hypomethylating agents, growth factors, immunotherapeutics, and biologic response modifiers have improved outcome in patients with lower-risk MDS (Buckner 2009), and the hypomethylating agent azacitidine, in particular, has been shown to prolong survival in patients with higher-risk disease (Fenaux 2009). Thus, for oncologists, it is important to diagnose and classify MDS early and to strategize to best utilize the range of treatments available. Further, in the current managed care environment, the outcome and survival benefits, patient expectations, and treatment protocols must be balanced with the need to manage costs.

In this article, I discuss the increasing success of novel therapeutics in slowing the progression of and improving the hematologic defects observed in higher-risk MDS and the issues that managed care organizations face regarding the role of these new agents in their institutional protocols and formularies.

Clinical features and diagnostic evaluation
MDS are disorders of blood; therefore, assessment is focused on hematologic analyses (Table 1). A complete blood count with examination of peripheral blood smear and platelet count is standard if MDS is suspected, particularly when looking for enlarged erythrocytes (treat-
Hematologic analyses are key to the identification of MDS

- CBC with differential, platelet count
- Serum FE, TIBC, ferritin, folic acid, B12
- LDH, haptoglobin, reticulocyte count, Coomb’s tests
- Baseline serum erythropoietin in the event growth factor therapy is considered
- Bone marrow studies
  - Aspirate
  - Biopsy
  - Cytogenetics

CBC=complete blood count, FE=iron, LDH=lactate dehydrogenase, MDS=myelodysplastic syndromes, TIBC=total iron-binding capacity. Source: NCCN 2009
associated risk for AML (Greenberg 1997, Mufti 2008a). This predictive model defines cytogenetic subgroups at diagnosis that, when combined with percentage of bone marrow blasts and number of cytopenias, designates good, intermediate, and poor risk for evolution to AML, and defines low, intermediate 1, intermediate 2, and higher-risk subgroups for survival, indicating progressively greater mortality risk (Table 2). Stratification for age further improves the prognostic significance of IPSS risk categories for survival. Based on these criteria, approximately 70 percent of patients will have low or intermediate 1 MDS at diagnosis, and 30 percent will have intermediate 2 or higher-risk disease and the associated risk for AML and reduced survival (Figure 1).

An alternative to the IPSS is the WHO-Based Prognostic Scoring System (WPPS), which takes into account red blood count (RBC) transfusion requirements rather than cytopenias to determine survival risk categories, making it a functional rather than laboratory assessment (Malcovati 2007). The inclusion of transfusion burden in the WPPS acknowledges an important step in the natural history of the disease and provides a means to follow patients for treatment response or disease progression, although the absence of criteria for thrombocytopения limits the usefulness of this tool.

IPSS features can be used as guidelines in selecting treatment. Lenalidomide (Revlimid), for example, is approved for subjects with transfusion-dependent anemia due to low and intermediate 1 MDS associated with del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, whereas the hypomethylating agents azacitidine (Vidaza) and decitabine (Dacogen) are indicated for low, intermediate, and higher-risk disease. Cytogenetic findings used in this prognosis classification scheme are also proving valuable in directing therapy; for example, MDS patients with deletion 5q mutation consistently respond to lenalidomide, making it the treatment of choice, and those with trisomy 8 have been shown to be sensitive to antithymocyte globulin (Galili 2007, NCCN 2009), whereas azacitidine, compared with the conventional care regimen, appears to work particularly well in patients with deletion 7q mutation (Mufti 2008b). Fenaux (2009) found that for patients with deletion 7q mutation, the median Kaplan-Meier overall survival (OS) increased from 4.6 months on conventional care (n=27) to 13.1 months with azacitidine therapy (n=30).

Treatment guidelines
In recommending treatment for clinically significant cytopenia(s), the National Comprehensive Cancer Network (NCCN) recognizes two major patient categories: Patients who are in the IPSS low and intermediate 1 categories, and those who are in the IPSS intermediate 2 and higher-risk cate-

![FIGURE 1](image-url)

**Survival and evolution to AML by IPSS classification**

From diagnosis in untreated patients. Kaplan Meier curves.

AML=acute myeloid leukemia, Int=intermediate, IPSS=International Prognostic Scoring System.

Source: Adapted from Greenberg 1997 with permission.

**TABLE 2**

<table>
<thead>
<tr>
<th>International Prognostic Scoring System (IPSS)</th>
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*Good=normal, -Y, del(5q), del(20q); Intermediate=other karyotypic abnormalities; Poor=complex (≥3 abnormalities) or chromosome 7 abnormalities.
†Hgb <10 g/dL; ANC <1800/µL; platelets <100,000/µL.
Source: Greenberg 1997
gories. In this article, I focus on the latter group and on allogeneic hematopoietic stem cell transplantation (HSCT); the hypomethylating agents azacitidine and decitabine, which are proving effective in treating higher-risk MDS; and on additional approaches under investigation.

**HSCT.** HSCT from a human leukocyte antigen-matched sibling donor is the only potential cure for patients with intermediate 2 or higher-risk MDS, although not all patients are candidates for this procedure. (Anderson 1997, Demuyck 1996, NCCN 2009, Nevill 1998, Scott 2006). Without HSCT, median survival after diagnosis of MDS is 4.6 years for patients under 60 years and significantly lower for those diagnosed after age 60 (Greenberg 1997). With HSCT, long-term survival rates as high as 70 percent have been reported (Cutler 2004, DeWitte 2000); however, because HSCT carries substantial risk for morbidity and mortality, including approximately 20 percent first-year mortality, it must be used with extreme caution, particularly in patients over age 60.

Cutler (2004) used a Markov model to determine best outcomes from three different timing strategies for HSCT in patients with MDS: 1) transplantation at diagnosis; 2) transplantation at progression to AML; and 3) transplantation at a fixed time in between. Analyses were carried out for all four IPSS stratification categories. The investigators found that optimal timing for HSCT depended on IPSS category. Because of the risk for morbidity and mortality with HSCT, patients with IPSS low or intermediate 1 MDS realized maximal life expectancy when transplantation was delayed but performed prior to the onset of AML. Among patients with IPSS intermediate 2 and higher-risk disease, performing transplantation at the time of diagnosis yielded best overall survival results, probably due to the advanced stage and higher risk for rapid progression associated with this status. Therefore, early and aggressive intervention with HSCT should be considered for eligible patients with higher-risk disease.

**Hypomethylating agents.** One of the mechanisms that may contribute to the development of MDS is the methylation of critical DNA sites involved in cellular transcription secondary to genetic damage, thereby blocking differentiation and maturation of the abnormal cells (Silverman 2001). It is thought that this process protects against the reproduction of damaged cells, but it has been proposed to inhibit tumor suppressor genes as well, thereby eliminating their protective capability. As a person ages, the amount of methylated DNA increases, but a reduction in tumor suppressor function means a simultaneous escape and multiplication of defective cells. Azacitidine and decitabine are two different cytosine analogues, but both with a nitrogen in place of the carbon grouping position 5 that prevents methylation. They are preferentially incorporated into DNA, and with azacitidine, also into RNA. Incorporation into DNA inactivates the methyl transferase enzyme and halts methylation of the gene, which allows previously inactivated DNA, now with unmethylated cytosine residues, to begin to be transcribed with restored tumor suppressor function and programmed apoptosis.

The U.S. Food and Drug Administration has approved azacitidine (Vidaza 2009) and decitabine (Dacogen 2009) for intermediate 2 and higher-risk MDS. Azacitidine is given on an outpatient basis at 75 mg/m²/day for 7 days and repeated every 28 days as a subcutaneous (SC) injection or a 10- to 40 minute intravenous (IV) infusion. Decitabine is approved for use as a 15 mg/m² IV infusion delivered over 3 hours every 8 hours for days 1-3 of every 6-week cycle, necessitating hospitalization for infusion during each treatment cycle.

**Azacitidine.** Fenaux (2009) recently evaluated azacitidine and compared its efficacy at 75 mg/m²/day given subcutaneously for 7 days and repeated every 28 days with three other conventional care regimens used to treat MDS — best supportive care (BSC), low-dose cytarabine, and intensive chemotherapy (the comparator option was selected by individual investigator choice) — in the treatment of 358 patients with higher-risk MDS. Because of the advanced age of the population (mean, 76 years) more subjects received BSC (n=105) or cytarabine (n=49) than the intensive chemotherapy regimen (n=25). The primary endpoint of the trial was OS (patients followed until death or study closure to ensure
maximal response); secondary endpoints included time to AML or death, infections requiring IV antimicrobials, transfusion independence, and hematologic response and safety. At the time of analysis, the patients had been followed for a median 21.1 months, with an observed median OS of 24.5 months in the azacitidine group and 15.0 months in the conventional care group (stratified log rank \( P = .0001 \)) (Figure 2, page 7). The survival advantage began early as the Kaplan-Meier survival curves separated permanently after only 3 months. At 2 years, 50.8 percent of azacitidine-treated patients were alive vs. 26.2 percent of those in the conventional care group (\( P < .0001 \)). This significant benefit for azacitidine was consistent across all MDS cytogenetic subtypes and all IPSS subgroups. In addition, the proportion of subjects with complete response (CR) or partial response (PR) was significantly greater with azacitidine therapy than with conventional care. Time to disease progression, rates of relapse after complete or partial remission, and death rates also were significantly better in the azacitidine group, as were proportions of erythroid and platelet improvements. There was no significant difference in the frequency of major neutrophil improvement between the two treatment groups. Peripheral blood cytopenias were the most common grade 3-4 adverse events in all treatment groups. These results substantiated a benefit for azacitidine in terms of increased overall survival and improved clinical and laboratory markers compared with conventional standards of care in patients with higher-risk MDS.

For patients who respond to azacitidine, treatment should be continued until there is evidence of disease progression or unacceptable toxicities develop. Also, it is important to note that responses to azacitidine may improve with continued treatment.

Decitabine. In a combined EORTC leukemia and German MDS Study Group randomized phase 3 trial (Wijermans 2008), investigators followed responses to low-dose decitabine (15 mg/m² IV over 4 hours every 8 hours for the first 3 days of an every 6-week cycle, maximum 8 cycles) versus supportive care in 233 patients aged ≥60 years with intermediate 2 or higher-risk MDS or CMML. Patients on supportive care returned for response monitoring every 24 weeks and patients who had any response to decitabine were re-assigned to two more cycles of therapy and then discontinued. Patients with progressive disease at the time of assessment were discontinued. The groups were well balanced for age, performance status, FAB criteria, cytogenetics, and IPSS classification. The median number of cycles administered was four, and 40 percent of patients received two cycles or less. The overall response rate was 34.5 percent, and progression-free survival (PFS) was significantly prolonged with decitabine therapy (0.55 vs. 0.25 years, \( P = .004 \)), but median OS times with decitabine did not improve significantly, at 0.84 years versus 0.71 years with supportive care (log rank 2-sided, \( P = .38 \)). The Kaplan-Meier OS curves are shown in Figure 3. The time to AML or death was not significantly different between groups (\( P = 0.24 \)). Toxicities were primarily hematologic, including grade 3-4 febrile neutropenia in 26 percent of decitabine-treated patients and 7 percent of the supportive care group. Grade 3-4 infections occurred in 59 percent and 47 percent of subjects, respectively.

Survival benefit. Overall, available data with hypomethylating agents indicate a survival benefit with azacitidine that has not been duplicated with decitabine. In Wijermans’ study (2008), the failure to achieve significant benefit in terms of OS with decitabine is consistent with the findings of a previous trial (Kantarjian 2006). This survival distinction, observed in clinical trials with the two agents, may suggest a preference for azacitidine in the treatment of MDS IPSS class intermediate 2 or higher-risk. MCOs should interpret data on cost, clinical benefit, survival, and quality of life (QoL) to make formulary and protocol decisions in line with institutional requirements and internally defined standards of care.
Other treatments. The NCCN (2009) recommends high-intensity chemotherapy regimens for patients with higher-risk MDS for whom a stem cell donor cannot be found or for those eligible for HSCT but who require blast reduction prior to the procedure. Due to the substantial morbidity and mortality associated with these regimens, the NCCN recommends that they be administered in the setting of a clinical trial. Comparative trials have not revealed any significant difference in outcomes with regimens based on idarubicin, cytarabine, fludarabine, or topotecan (Estey 2001). Furthermore, there is a strong likelihood of multidrug resistance in advanced MDS, leading to poorer response rates and abbreviated response durations (Estey 2001, Sonneveld 1993). Ongoing clinical trials also are examining the potential of multidrug resistance modulators, and may define a role for these agents in the future.

Future therapeutic directions

Several therapeutic methods to achieve better outcomes in higher-risk MDS are currently in the research phase. Combination therapy, long-term maintenance regimens, and such novel agents as clofarabine are among the more promising.

Maintenance therapy. Despite a 50 percent response rate to induction chemotherapy among patients with higher-risk MDS, response duration generally is short and survival brief. To assess the benefit and risks of extending hypomethylating therapy for long-term maintenance therapy, the Nordic MDS Group in Sweden (Grövdal 2008) carried out a prospective multicenter phase 2 study delivering low-dose azacitidine (mean dose, 54.3 mg/m^2) administered for 5 of 28 days (until relapse or unacceptable toxicity) to 23 of 60 patients with higher-risk MDS (n=23) or AML (n=37) and who achieved a CR after induction therapy with daunorubicin and cytarabine, also known as ara-C. Subjects were ineligible for stem cell transplantation. With maintenance therapy for a median of 13.5 months, the median OS was 20 months, and 11 of 24 patients experienced no adverse events. At last follow-up, three patients were still in CR. The most commonly reported side effect was mild rash at the injection site. These results suggest that maintenance therapy with azacitidine can prolong survival in patients with higher-risk MDS.

Combination therapy. Resistance to hypomethylating agents is an emerging clinical concern. In phase 1/2 clinical studies, histone deacetylase inhibitors appeared to improve the activity of hypomethylating agents when given in combination. In a recent phase 3 trial, however, the combination of decitabine plus valproic acid offered no significant response benefit over decitabine alone in the treatment of 72 patients with MDS or AML (Issa 2008).

On the other hand, early results are promising for the combination of azacitidine plus vorinostat, an alternative histone deacetylase inhibitor. In a phase 1 study by Silverman (2008), azacitidine (55 or 75 mg/m^2 SC) plus vorinostat (200 or 300 mg by mouth) was administered in eight different dosage and schedule combinations to 23 patients with MDL or AML. A minimum of four 28-day cycles was scheduled. At analysis, 50 percent of subjects had achieved CR and 11 percent CR with incomplete blood count recovery, which is superior to results reported with either agent alone and to other hypomethylating agent/histone deacetylase inhibitor combinations. The overall response rate (ORR) was 83.3 percent. Fatigue was related to duration of vorinostat exposure and not to total daily dose. These results suggested the combination was safe and effective, and it is now scheduled for phase 2 investigation.

In addition, the complementary benefits of a combination of lenalidomide, which has immunomodulatory, anti-angiogenic, and cytotoxic properties, and azacitidine, with cytotoxic effects and hypomethylating activity, have been examined in 19 patients with MDS, and early data suggest that the combination appeared to be well-tolerated, with efficacy superior to either agents’ single-agent activity in higher-risk MDS (Sekeres 2008).

Clofarabine. Clofarabine (Clolar), a second-generation purine analog FDA-approved for treating acute lymphoblastic leukemia, is also now being used to treat MDS. It has demonstrated high response rates as first-line therapy for patients over age 60 with AML (ORR: 46 percent; CR: 38 percent), and proven active in patients over age 70 with poor-risk cytogenetics and poor performance status (Erba 2008). It is currently being studied in both IV (15 mg/m^2 vs. 30 mg/m^2/day for 5 days every 4 to 6 weeks) and oral (40 mg/m^2/day for 5 days, reduced to 30 mg/m^2/day after first 6 patients had been treated on the higher dose) formulations for the treatment of patients with ≥5 percent blasts and higher-risk MDS (Faderl 2008). Early results presented at the 2008 American Society of Hematology meeting reveal ORRs approaching 50 percent with both oral and low-dose IV formulations with efficacy in one quarter to one third of patients who failed hypomethylating therapy (Faderl 2008). Liver complications may be a concern and patients warrant regular testing.

Alternative outcomes

A number of additional factors can influence the natural history of MDS, and the success and cost of therapy have been identified and should be taken into account in making decisions regarding treatment protocols and formulary approval for the available medications for intermediate 2 and higher-risk MDS patients. These factors are discussed below.

Transfusion requirement. A high transfusion burden (≥2 transfusion events in an 8-week period) is a rec-
ognized marker of disease severity and worse prognosis in MDS. Malcovati (2006) showed that increased transfusion burden can be directly correlated with risk for disease progression and survival. The investigators reported that increasing transfusion dependency predicted a greater risk for transition to leukemia and decreased survival. It is not clear whether the increased death is due directly to more severe MDS, to the underlying anemia, or to a consequence of regular transfusions (e.g., iron accumulation), but it is likely a combination of the three. This relationship, however, formed the basis for the WPSS prognostic schema (Greenburg 1997, Mufti 2008a).

Importantly, effective hypomethylating therapy may induce transfusion independence and reduce morbidity and mortality risk in patients with higher-risk MDS. Fenaux (2009) reported that 45 percent of patients who required RBC transfusions on enrollment became RBC transfusion independent while receiving azacitidine therapy; among subjects receiving conventional care, only 11.4 percent achieved RBC transfusion independence (P<.0001). Even more compelling, it was noted that among patients who did not require transfusions on entry, 85.3 percent of azacitidine-treated patients maintained RBC transfusion independence over the course of the trial compared to 56.9 percent receiving conventional therapeutic approaches. In a study by Kantarjian (2006) involving decitabine therapy, RBC transfusion independence increased progressively with each cycle of decitabine therapy, while the RBC transfusion requirement did not change significantly among patients treated with supportive care.

RBC transfusion is a generally well-tolerated procedure that effectively increases the oxygen-carrying capacity of the blood. The most significant risks associated with this technique are volume overload, iron overload, infection, and, in immunocompromised patients, a small risk for graft-versus-host disease. Once a patient requires platelet transfusion, however, the prognosis worsens. Platelets, unlike RBCs, are highly immunogenic, leading to antibody development and self-destruction of infused platelets if human leukocyte antigen-matched donor cells are not used. Spontaneous and difficult to control bleeding can arise, and death usually occurs within a year.

**Treatment-related cytopenias.** Anemia, neutropenia, and thrombocytopenia may be worsened early in the course of hypomethylating agent therapy. With azacitidine therapy, in most cases cytopenias will resolve after one or two cycles of therapy, although this has not been shown with decitabine. In later cycles, the rates of these cytopenias diminish substantially, and therapy can be continued with few or no symptoms (Fenaux 2009).

**Infection.** The cytopenias associated with MDS place a patient at increased risk for infection, requiring increased resources and greater cost. Complications like bacterial pneumonia and skin abscess are not uncommon. Infection may be a frequent cause of death among patients with MDS, and in one study (Pomeroy 1991) accounted for more deaths than acute leukemia. As a result, aggressive treatment with antimicrobial therapy should be administered either prophylactically or at the first sign of infection to minimize the risk for severe, life-threatening complications. Treatment with azacitidine appears to reduce the risk for infection requiring IV antimicrobials by 33 percent compared with conventional care approaches (Figure 4). When measured as the rate of infection requiring IV antimicrobial therapy in patient-years of care, azacitidine had a 0.16 risk compared with 0.24 (P=.0032) for conventional interventions (Fenaux 2009). Comparable data do not exist for decitabine.

**Hospitalization.** In a French observational study to determine the daily practices for care of patients with MDS, Kelaidi (2008) reported the characteristics of 919 patients seen over a 1-week period in 74 centers in France: 13 percent of subjects were hospitalized, 4.5 percent for infections or bleeding and 8.5 percent for “active” treatment. In addition, 46 percent were being seen in day care (outpatient) facilities, predominantly for transfusions (40 percent). Only 40 percent of higher-risk patients were receiving EPAs. The authors concluded that active treatments are underprescribed in this population.

Several preventive or proactive interventions may help to reduce the need for hospitalization or acute day care and their associated high costs in patients with MDS. First, use of growth factor support or EPA at the first sign of neutropenia or anemia could prevent later need for hospitalization (Stasi 2005). Similarly, prophylactic antibiotics may prevent or diminish infection or pneumonia risk. When transfusion is necessary, if undertaken early it might be accomplished in the outpatient department,
with a relative reduction in cost compared with an in-patient procedure. In addition, there is a need to study revised regimens for active treatment that could reduce medical costs without impacting patient benefit. Azacitidine, for one, is being studied (Lyons 2009) as an ongoing 5-day regimen for lower-risk MDS that may reduce the need for weekend care and may have the simultaneous benefit of decreasing clinic and hospitalization fees. If significant efficacy and survival benefit also is established, these improvements may prove one agent more cost-effective than another.

Conclusion
For patients classified as intermediate 2 or higher-risk MDS, early diagnosis and treatment initiation are important factors for deterring disease progression and prolonging survival. A clinical and hematologic laboratory diagnosis should be confirmed with bone marrow morphologic studies. HSCT should be considered at diagnosis for optimal outcomes in patients with intermediate 2 and higher-risk MDS who are appropriate candidates for HSCT. Patients with lower-risk disease do better when transplant is delayed, as long as it is undertaken before progression to AML. The hypomethylating agents azacitidine and decitabine have been shown to alter some of the hematologic defects of the disease in patients with higher-risk MDS, and azacitidine has shown survival benefit.

Ongoing maintenance therapy may be essential to long-term disease control in these patients, unless there are signs of disease progression, and this approach is under investigation in clinical trials. Early results of studies undertaken suggest that long-term maintenance therapy with azacitidine after response to induction chemotherapy improves survival in patients with higher-risk MDS. Regimens that combine agents with different mechanisms also are being studied as a means to prolong responses and sustain survival in MDS patients. The cost of therapy can be contained through a concerted effort to focus on outpatient treatment, manage cytopenias and infections quickly, and minimize hospitalizations.

MCO decision makers should evaluate all available data on agents proven effective in treating higher-risk MDS within the context of their institutional guidelines and standards of care to define a treatment protocol. Their assessment should consider clinical benefit (in terms of transfusion burden, need for antimicrobials, and hospitalization rate), survival outcomes, and QoL as well as cost. Medication choice requires a well-orchestrated collaboration among patient, physician, and payer to maximize outcome within reasonable cost boundaries.

References


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Disclosure: Bart L. Scott, MD, states that he is a consultant to Celgene Corp. and is on the speakers bureau of Alexion Pharmaceuticals.
DISCUSSION

STEVEN R. PESKIN, MD: Decitabine has a different dosing protocol and schedule compared with azacitidine. Dr. Scott, can you clarify that difference?

BART L. SCOTT, MD: Decitabine is given as a continuous IV infusion over 3 hours repeated every 8 hours for 3 days, which requires hospitalization. Azacitidine, at a starting dose of 75 mg/m² once daily for 7 days and repeated every 4 weeks, can be given either IV or SC on an outpatient basis, which requires about a 1-2 hour-long outpatient visit. But with the infusion, a nurse has to check vital signs, get the IV started, and monitor the patient, so that takes about 2 to 3 hours. Some practitioners give decitabine as 20 mg/m² in a 1-hour IV infusion daily for 5 consecutive days, thereby mitigating the need for hospitalization. However, that regimen has not been compared with the FDA-approved dose.

PESKIN: Why would you choose IV delivery?

SCOTT: Patients who already have a line in place would probably receive the IV. If they have a very low platelet count, say <50,000, my preference is to give an IV to avoid bruising and bleeding. Otherwise, SC delivery is generally preferred, because it is faster, easier, and less expensive. Now if a patient tells me that he or she has an absolute phobia regarding shots, then I have to give an IV.

PESKIN: What was the rationale for studying long-term maintenance therapy after maximum response with a hypomethylating agent?

SCOTT: One of the important things that has come out of the hypomethylating agents literature is that if a patient has a response, it’s a good idea to continue the medication. In the Fenaux study [2009], of the 175 patients who received azacitidine, 51 percent had an International Working Group (IWG) response*, but continued dosing led to a higher IWG response in 48 percent of the patients. In anecdotal reports, discontinuation of azacitidine after patients achieve a response is often followed by disease progression. A design flaw may have contributed to poor outcomes with decitabine in the Wijermans study [2008]; patients who had a complete remission were taken off the study after an additional two cycles of treatment.

PESKIN: You mentioned that in the Fenaux study [2009] cytopenias worsened with azacitidine. The neutropenia rate (Grade 3/4) was 61 percent versus 21 percent with best supportive care, and greater thrombocytopenia, leukopenia, and anemia, as well. Was this a side effect or did the medication not work?

SCOTT: Those data are correct, but remember that the cytopenias that occur during the first 2 months of treatment with azacitidine usually resolve over time, and later treatment does not induce hematologic toxicity. This finding is believed to be due to loss of the MDS clone on which the patient has been dependent, and a delay until normal stem cells start working again. In fact, these MDS malignant clones actually down-regulate the production of normal stem cells, and so are especially insidious. But the risks from these cytopenias are minor. Hospital admissions for IV antimicrobials during early azacitidine therapy, for instance, do not differ much from those with conventional care, and infection rates may, in fact, be lower. There are two ways to approach this early toxicity: First, forewarn patients — be honest with them. Explain that their hematological counts will get a bit worse during the first two cycles, but after that, the counts will rise and they will feel better. Second, provide support therapies at the first sign of cytopenia. If a patient develops neutopenia, consider a prophylactic antibiotic or antiviral agent. Also, although the azacitidine PI recommends delaying treatment in the event of cytopenias, I use my judgment and try to keep on schedule.

DAVID FRAME, PHARMD: When these drugs first came out, it was common to delay cycles, but now that we have more experience, many people will push through as long as the cytopenias are not too severe. In fact, you actually get to the endpoint faster if you do. The longer you delay, the more methylation comes back, so it’s like starting over again. Therefore, what normally takes four cycles can actually require six, seven, or even nine cycles of therapy to reach best response.

ALLAN JAY KOGAN, MD: But we need standards that are written and consistent. It is very difficult to establish prior authorization criteria if standards are not documented and agreed upon. Using a package of care, i.e., an acknowledged and evidence-based agenda of approved potential treatments, including adverse event resolution therapies, to address potential treatment adjustments would allow employers, for example, to anticipate the bill that’s coming. They need to know if the billing from a particular therapy might be much higher than by following the PI.

SCOTT: But we don’t know what led the FDA at the time of azacitidine approval to require dosing delays in the PI dosing guidelines. The data we now have suggest you should not delay. If the NCCN would corroborate this position, I think we can agree that this is the standard of care and inform the FDA accordingly.

PESKIN: What are the key issues addressed by Dr. Scott that would be of greatest interest to MCOs?

KOGAN: The first is accurate diagnosis. We want to identify the best return on investment on any intervention so we do not treat 100 people to achieve the desired outcome in 30. We would like to ensure targeted medicine,

* In 2000, the IWG proposed standardized criteria for evaluating clinically significant responses in patients with MDS. See Cheson 2000.
even if it requires treatment at specialty centers, or what we in the payer community call “centers of excellence.” We want to ensure that we are treating the right population and not dosing everybody to improve a few.

JEFFREY D. DUNN, PHARMD: The key trials are important to decision makers at SelectHealth, but the final protocols and formulary choices need to be collaborative. A multidisciplinary group including representatives from community oncology and academic groups, the P&T, and financial people would all contribute to a final decision. For instance, altering the decitabine dose without a published data comparison with the approved regimen may cut costs, but is it the right thing to do? We need a diverse and well-rounded team to agree on those decisions.

PESKIN: Can you think of any analogous situations — e.g., multiple sclerosis, rheumatoid arthritis, or Parkinson’s — in which novel treatments like injectable biologics have altered the way we should think about treatment and reimbursement?

DUNN: If you look at the three big cost categories in the injectable infusible arena, it’s oncology, MS, and RA. There were financial incentives for rheumatologists to infuse infliximab (Remicade) in their office versus prescribing a SC. But oncology is more political due to the life and death impact of decisions. Can cost be the primary factor in those decisions?

KOGAN: About 80 percent of oncologists’ revenue comes from infusions given in their offices. So an oncologist doesn’t want to put patients in the hospital. This is one area in which MCO and provider needs meet.

KIRBY ENG, RPh: The market is creating collaborations among community-based oncologists, hematologists, and payers. The easiest way to save money is to simply reduce physician drug reimbursement fees, but payers have to create a delicate balance if they want to maintain a healthy provider network.

PESKIN: When you look at the decitabine versus azacitidine trials, a notable difference is that growth factor use was not allowed in the azacitidine trial, but the decitabine trials allowed G-CSF growth factor and EPO. In the Phase 3 decitabine trials, about 45 percent of patients on decitabine ended up receiving growth factor and EPO. In the Phase 3 decitabine trials, about 45 percent of patients on decitabine ended up receiving growth factor and EPO. What are the implications of this difference?

SCOTT: Based on current data, for the patient who has isolated anemia with less than 5 percent bone marrow blasts, no sign of genetic abnormalities, and erythropoietin <500, in my opinion ESAs remain the agent of choice. But in the same patient with a proven deletion 7q mutation, azacitidine therapy would be appropriate for front-line therapy. There’s no prospective randomized study showing that ESAs prolong survival. A retrospective study [Jädersten 2008] showed that patients who received ESA therapy had prolonged survival compared with patients who did not, and, anecdotally, improved functionality and QoL.

PESKIN: Clofarabine is being used more commonly in MDS and leukemia patients, but since it is FDA-approved only for acute lymphoblastic leukemia, will there be reimbursement challenges?

SCOTT: Yes, patients are already having difficulty with reimbursement. An oral formulation is being developed, which will simplify administration, but complicate the reimbursement issue further. In addition, a histone deacetylase inhibitor, aurora kinase inhibitor, and Jak2/Flt-3 inhibitor are all in the pipeline. But for now, azacitidine is the only agent that has been shown in a randomized study to prolong survival in MDS, and it is FDA-approved.

SCOTT: EPO is frequently used as first-line therapy for anemia. It works very well, but it doesn’t have a durable response. Eventually patients become RBC transfusion dependent. In a few cases, patients who were treated with azacitidine and EPO added at a later point, the hemoglobin and hematocrit appeared to increase dramatically. It is theoretically possible that azacitidine led to a restoration of response to the erythroid-stimulating agent (ESA) — azacitidine works by manipulating gene production and influences cellular morphology, which then restores response to EPO. This relationship would be worth investigating further.

KOGAN: This returns to the package of care issue that I mentioned — considering not only drug therapy but supportive therapies as well and how those are managed. It is not an insignificant cost factor, so we must consider the proper utilization and potential costs of all possible interventions.

FRAME: When we look at the azacitidine data in lower-risk patients from a managed care perspective, in the CALGB trial [Silverman 2008], a fair number of low and intermediate 1 patients were included, and they had extremely good responses. I hope there will be more research that focuses on the use of hypomethylating agents in the lower-risk group. From a biologic standpoint, it makes sense that if we change the biology earlier, we might be able to prolong survival even further. On the other hand, that raises the concern that rather than treating patients with these medications for 24 months, treatment might continue for 5 to 7 years.

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Alternative Dosing Schedules for Methylation Inhibitors in MDS Treatment

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KEY POINTS
• Dose schedules that include inpatient and weekend therapy have an enormous impact on treatment-related costs and should be a key consideration in evaluating MDS treatment regimens.
• Alternate dosing schedules for azacitidine and decitabine are being explored to avoid weekend therapy and inpatient hospitalization.
• Although no clinical trials have yet compared alternate dosing regimens for azacitidine and decitabine and their efficacy with the FDA-approved regimens, the choice of an agent to treat higher-risk MDS should consider survival advantage.

The DNA hypomethylating agents azacitidine (Vidaza) and decitabine (Dacogen) are proving effective in treating myelodysplastic syndromes (MDS) by successfully mitigating cytopenias, decreasing transfusion dependence, increasing the time until progression to acute myeloid leukemia (AML), and generally improving quality of life (QoL) in patients with all five French-American-British (FAB) subtypes and both lower- and higher-risk International Prognostic Scoring System (IPSS) disease (Fenaux 2009, Kantarjian 2006, Silverman 2002, Wijermans 2008). Yet, complicated or inconvenient administration requirements may interfere with the acceptance of or adherence to these medications by both patients and physicians.

Azacitidine has been shown in a phase 3 randomized trial to significantly prolong survival in intermediate 2 and higher-risk MDS patients (Fenaux 2009); thereby altering the natural history of the disease. The U. S. Food and Drug Administration-approved schedule for azacitidine is a subcutaneous (SC) injection at 75 mg/m² given once daily for 7 days (every 28-day cycle) (Vidaza 2008), which requires administration over a weekend — a service many clinics do not provide. Decitabine is FDA-approved as a 3-hour intravenous (IV) infusion of 15 mg/m² repeated every 8 hours for 3 days (every 6-week cycle) (Dacogen 2006), which necessitates hospitalization during each treatment cycle. These demands on patient and medical resources can negatively impact the acceptability of treatment and adherence to a treatment regimen. As a result, revised treatment schedules are being considered. It is important to recognize, however, that the dose and schedule approved by the FDA and available for widespread clinical use cannot simply be altered for convenience — any revised protocols must show, on the basis of randomized clinical trials, that the alternative dosing regimen yields equivalent or better efficacy and safety than the FDA-approved dose and schedule.

Most patients prefer a therapy with greater ease of administration. However, optimal treatment goals cannot be sacrificed. Such issues as survival benefit, transfusion independence, complications of therapy, and need for hospitalization for adverse events (AEs) also weigh into the selection of a preferred treatment regimen. Thus, administration protocols for azacitidine and decitabine usage to treat MDS should attempt to increase patient convenience along with preserving or improving efficacy and safety within cost-control boundaries.

Clinical trials to evaluate alternative administration routes must be compared with the current FDA-approved regimens. In phase 3 trials, only SC azacitidine has shown an established survival advantage and improved time to AML in higher-risk MDS compared with conventional care regimens (Fenaux 2009); therefore, any future trials of either azacitidine or decitabine should be compared with the 7-day regimen of SC azacitidine. It is important to understand that pharmacologically,

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these drugs are not the same. Azacitidine contains the ribonucleotide sugar, which is partially metabolized to the deoxynucleotide, allowing azacitidine to be incorporated into RNA and DNA, whereas, decitabine contains the deoxynucleotide sugar and is incorporated only into DNA. This may suggest some added influence of RNA hypomethylation on the activity of azacitidine (Glover 1987).

**Alternative dosing schedules**

Given the challenges associated with the administration of azacitidine and decitabine, the protocols used in clinical practice have begun to vary from that recommended in the FDA-approved prescribing information. As a result, other regimens are being explored. For example, to avoid weekend therapy, azacitidine is being studied as either a 5-day schedule or a 5-2-2 schedule — that is, treatment is administered for 5 days during the first week, 2 days of the weekend are skipped, and the patient returns for the final two SC injections on the first 2 consecutive days of the next week, which is repeated on a 28-day schedule. Similarly, some investigators have begun to test once-daily decitabine at an increased dose of 20 mg/m² by 1-hour IV infusion for 5 consecutive days repeated every 4 weeks, delivered on an outpatient basis. Results from clinical trials formally investigating the outcomes and safety associated with each of these alternative regimens have been recently published and are discussed below.

**Azacitidine.** Lyons (2009) reported preliminary results from a phase 2 study exploring three alternative azacitidine (AZA) regimens designed to avoid weekend dosing in the treatment of 151 patients with MDS (Figure 1). Patients were randomly assigned to one of the following: AZA 5-2-2 (75 mg/m²/day SC for 5 days, followed by 2 days no treatment, then 75 mg/m²/day for 2 days); AZA 5-2-5 (50 mg/m²/day SC for 5 days, followed by 2 days no treatment, then 50 mg/m²/day for 5 days); or AZA 5 (75 mg/m²/day SC for 5 days). All regimens were repeated every 4 weeks for six cycles during the treatment phase. After two cycles, dose adjustments were allowed based on response and/or toxicities. Erythropoiesis-stimulating agents (ESAs) could be continued if used prior to enrollment, but not started anew. Primary endpoints were hematologic improvement and red blood cell (RBC) transfusion independence. A total of 139 patients (92 percent) received at least two treatment cycles and 79 (52 percent) completed all six cycles. Hematologic improvement was observed in 44 percent, 44 percent, and 46 percent; major platelet improvement occurred in 43 percent, 27 percent, and 50 percent; and major neutrophil improvement occurred in 17 percent, 17 percent, and 38 percent in the AZA 5-2-2, AZA 5-2-5, and AZA 5 arms, respectively.

Among patients who were RBC transfusion dependent at baseline, 50 percent, 55 percent, and 64 percent of patients treated with AZA 5-2-2, AZA 5-2-5, and AZA 5, respectively, achieved transfusion independence within six cycles. A subanalysis (Lyons 2009) showed that the absence of baseline neutropenia or thrombocytopenia, as well as lower baseline transfusion requirement, was associated with a higher rate of RBC transfusion independence during treatment. Responding patients tended to be FAB lower-risk patients, including 9 of 12 (75 percent), 6 of 12 (50 percent), and 11 of 16 (69 percent) patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing groups, respectively. Grade 3-4 hematologic toxicity was nearly doubled on the AZA 5-2-2 regimen (66 percent) compared with the 5-day regimen (34 percent), and with the AZA 5-2-5 regimen falling in the middle (50 percent), suggesting a benefit in terms of toxicity with the AZA 5-day schedule.

The population enrolled in this trial was mostly of FAB lower-risk disease status (63 percent) or refractory anemia with excess blasts (30 percent); therefore, interpretation about efficacy of the altered schedules in patients with higher-risk disease is not possible. Another limitation of the trial is that the FDA-approved course of 7 consecutive days of treatment was not included as a comparator, so although the efficacy appears to be consistent with outcomes achieved with the FDA-approved dose and schedule, equivalence cannot be concluded. Also, the trial was not powered to compare outcomes among...
the three alternative dosing regimens, so the data demonstrated only that each alternative dosing regimen administered improved the endpoints investigated. Clearly, these issues will have to be resolved in a phase 3 trial. In the meantime, this trial is being extended into a maintenance treatment phase, offering continuing patients AZA 75 mg/m²/day administered SC for 5 days, repeated every 28 days or every 42 days, to determine the durability of hematologic responses with long-term AZA maintenance therapy.

**Decitabine.** In the ADOPT trial (Steensma 2009a), a group from the Mayo Clinic examined an alternative dosing schedule for decitabine of 20 mg/m² delivered as a 1-hour IV infusion daily for 5 consecutive days and repeated every 4 weeks — a regimen conducive to outpatient therapy — in the treatment of MDS patients with an IPSS score > 0.5 (Figure 2). There were 99 patients enrolled in the study, median age 72 years, who were examined for the primary endpoint of overall response rate (ORR) by International Working Group (Cheson 2003) criteria and secondary endpoints of cytogenic response, hematologic improvement, response duration, survival, and safety.

At the end of a median of 5 cycles, the ORR was 32 percent, comprising 17 percent complete responses (CRs) and 15 percent marrow CRs (mCRs), which included 18 percent hematologic improvement (HI). mCR is defined by ≥50 percent myeloblast reduction from more than 5 percent myeloblasts to ≤5 percent, but without recovery of peripheral counts to a level meeting criteria for CR. Responses occurred by the end of cycle 2 in 82 percent of subjects who responded. Similar response rates were observed in all IPSS risk categories. Median survival was 19.4 months. Among patients who entered the study requiring RBC or platelet transfusions, 33 percent converted to RBC and 40 percent to platelet transfusion independence on therapy. These rates were lower than those reported in the azacitidine trials (Lyons 2009, Feinaux 2009, Silverman 2008). Hematologic toxicity was high in this study; 31 percent of patients experienced Grade 3 or higher neutropenia (14 percent febrile neutropenia), 18 percent thrombocytopenia, and 12 percent anemia. Importantly, 65 percent of patients required hospitalization during the study. Thus, although the investigators concluded that a 5-day outpatient schedule of decitabine provided meaningful clinical benefit, the hematologic toxicity was more severe than that noted with the FDA-approved regimen, which requires excess hospitalization, and, in some cases, necessitated concomitant antimicrobial therapy.

**TABLE**

Results from two studies with DEC approved 3-day schedule and two studies with DEC 5-day outpatient alternative schedule

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<tr>
<th></th>
<th>Median # of cycles</th>
<th>Overall CR (%)</th>
<th>Overall improvement (%)</th>
<th>Time to AML or Progression-free survival (months)</th>
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<td>15</td>
<td>43</td>
<td>12.1</td>
<td>8.1</td>
<td>17.8</td>
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<tr>
<td>ID03-0180 (N=93)</td>
<td>7</td>
<td>37</td>
<td>65</td>
<td>15.2</td>
<td>9.2</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*As measured by IWG 2000 criteria; Patients who became RBC transfusion independent while on-study.

AML=acute myeloid leukemia, CR=complete response, DEC=decitabine, RBC=red blood cell.

Source: Adapted from Steensma 2009b
Several concerns have been noted about the design of this trial. As in the Lyons azacitidine study (2009), the standard of care was not used as a comparator, which did not allow conclusions to be drawn about relative efficacy and safety. Furthermore, the FDA-approved dose and schedule of decitabine was not used. The majority of patients in this study fell into the intermediate 1 risk category; thus, these results also cannot be extrapolated to a higher-risk MDS population. In addition, a cost analysis will have to be carried out to determine the savings achieved if a regimen is revised from inpatient administration to outpatient therapy, but the toxicity necessitated hospitalization of 65 percent of patients.

Steenmsa (2009b) compared results from two randomized phase 3 studies in which patients were assigned to the inpatient 3-day dosing schedule of decitabine versus supportive care with results from two phase 2 studies in which patients received the outpatient 5-day dosing schedule (Table, page 17). This comparison was not a meta-analysis and did not take into account the difference in design or protocol requirements, but the comparison revealed some interesting findings. The review suggested comparable overall improvement (CR + partial response [PR] + HI), time to AML or death, and progression-free survival (PFS) across all trials and both regimens (Table 1, page 17), with one additional decitabine treatment cycle accomplished with the 5-day lower dose schedule. The PFS and time to AML or death was approximately 2 months longer with the 5-day alternative schedule. Overall survival was 10 to 12.8 months with the FDA-approved schedule versus 17.8 to >20 months with the alternative schedule. Conversion to RBC transfusion independence was similar between schedules. These findings suggest some advantage associated with the 5-day protocol, but this must be weighed against the increased risk for hematologic toxicity, higher hospitalization rate, and associated costs observed in the ADOPT trial with the abbreviated outpatient schedule (Steenmsa 2009a).

Decision-making considerations

Given the data accumulated on the use of azacitidine or decitabine in the treatment of higher-risk MDS, there are several factors that should be included in a comparative analysis of the two drugs. These considerations include efficacy and safety data, inpatient versus outpatient treatment demands, and the ease and timing of medication administration.

The efficacy and safety data suggest that azacitidine is consistently effective and safe, with a proven survival advantage in patients with higher-risk MDS, whereas in studies done to date, decitabine has failed to significantly increase survival and has induced significant toxicity and substantial hospitalization when given on the abbreviated outpatient regimen. In comparing the delivery methods for the two agents, the FDA-approved administration of decitabine infusion requires hospitalization, with the attendant increased resource utilization and cost, whereas the traditional protocol for azacitidine is an outpatient SC injection or IV infusion. In studies of alternative regimens that are intended to improve patient and physician convenience, a 5-day/1-hour daily infusion of decitabine was feasible as an outpatient regimen, but was associated with significant neutropenia and substantial risk for febrile neutropenia, leading to a high hospitalization rate and associated costs.

Investigation into an alternative 5-day azacitidine schedule suggested good efficacy and safety in lower-risk patients, particularly in terms of transition to transfusion independence, which, if confirmed in a phase 3 trial with comparison to the FDA-approved 7-day schedule, may offer improved convenience and cost savings.

Treatment decisions. Treatment decisions and formulary development are based on several factors, including evidence of efficacy and safety of available medications, timing and schedule of medication delivery, convenience and ease of administration, and overall costs and resource utilization involved in different medication regimens. In the class of methylation inhibitors for intermediate 2/high-risk MDS, these issues are complicated by the risks associated with hematologic impairment in a disease such as MDS, including transfusion dependence and risk for infection, as well as the limitations associated with the recent addition of medications to the existing armamentarium for this disease. The administration schedule and delivery methods for both methylation inhibitors currently being studied in higher-risk MDS, as recommended in the prescribing information, involve substantial logistic and economic challenges. Both azacitidine and decitabine were approved with demanding regimens: azacitidine necessitating weekend therapy, and decitabine infusion requiring hospitalization. Yet, the FDA-approved azacitidine regimen is based on outpatient clinical trial experience and does not require hospitalization, whereas decitabine is approved only as a 3-day inpatient regimen, which necessitates inpatient (hospitalization) treatment.

Because of the concerns about schedule acceptability and cost limitations driven by the delivery methods for both drugs, two studies have been undertaken to improve the regimens to avoid weekend therapy or inpatient administration (Lyons 2009, Steensma 2009a, Steensma 2009b). The alternative regimens for both hypomethylating agents appear to offer activity in MDS consistent with that observed in the standard regimen; however, neither clinical trial was designed with the approved regimen as a comparator, and both involved predominantly lower-
risk patients. These limitations, therefore, do not allow conclusions about the benefit of the alternative dosing schedules in patients with advanced MDS or about equivalent efficacy and safety relative to the FDA-approved regimen for each drug. However, the approved azacitidine regimen has been shown to significantly increase overall survival in higher-risk MDS compared with conventional care regimens (Lyons 2009), whereas decitabine treatment has not shown that result, nor have any of the alternative dosing regimens with azacitidine or decitabine.

**Conclusion**

No randomized, comparative trials of the two methylation inhibitors azacitidine and decitabine have been undertaken; therefore, the choice of agent to treat higher-risk MDS should depend on the best outcome desired — survival advantage, which is the most clinically meaningful outcome in higher-risk MDS. MCOs are concerned about drug and administration costs, safety, hospitalizations, and adverse events, and these considerations factor into therapeutic decisions. Although the current FDA-approved regimens for azacitidine and decitabine may not be practical, it is important to realize that none of the trials evaluating alternative dosing strategies have yet been compared with the FDA-approved regimens studied in randomized trials, and that the populations, in general, are different. Phase 3 comparative studies of these alternative regimens, if implemented, may reveal similar efficacy, safety, and cost benefits. However, based on established trial results to date, azacitidine appears to be the preferred agent for treating intermediate 2 and higher-risk MDS.

**References**


**DISCUSSION**

STEVEN R. PESKIN, MD: In the ADOPT study, one of the endpoints was marrow complete response, a term I am not familiar with. Dr. Scott, can you explain what this criterion means clinically?

BART L. SCOTT, MD: Marrow complete response is marked by a reduction in the percentage of blasts in the marrow to <5 percent, without necessarily evidence of concomitant hematologic improvement. Theoretically, this improvement should correlate with a reduced risk of MDS progression. Although the relationship has not been confirmed in a clinical trial, there are anecdotal reports of marrow responses advancing to hematologic improvement with continued exposure to medication.

PESKIN: Is it possible that it indicates an actual change in the biology of the cells, and that addition of a growth factor, like interferon, might push those patients into hematologic response?

DAVID FRAME, PHARMD: Yes, exactly.

PESKIN: Based on Dr. Frame’s presentation, does anyone want to share thoughts about how site of care, route of administration, timing, or AEs influence preferred protocols or reimbursement decisions?

JEFFREY D. DUNN, PHARMD: There are several factors that would feed into our decisions at SelectHealth. First, we generally would prefer a SC route of administration over IV. This would enable us to keep people out of hospital as much as possible. The biggest concern with these alternative-dosing regimens is that they remain off-label. We need to garner support to get those protocols in the guidelines before we can implement those schedules.

ALLAN JAY KOGAN, MD: I agree. As payers, we have to...
be consistent, objective, and evidence-based, so that when we make a decision, it is based on something that’s transferable. In the payer community, we need to hold true to national standards of care. Our members all expect the same quality of care at the same cost. But if we can generate a revised algorithm — for example, develop a standardized off-label policy or gain approval from the FDA — then we can support the alternate protocol nationwide.

**PESKIN:** How about longitudinally? How do the data influence managed care strategies for the longer term?

**DUNN:** There are very few issues that we think about longitudinally in the payer community. We revise our employer relationships at no more than 6-month intervals, and there is little room to think about cost savings or better results 5 or 10 years down the road. For MDS policy, it is particularly complicated, because you must consider not just the cost of medication, but inpatient versus outpatient treatment, management of adverse events, and adjunctive therapies like ESAs and stem cell transplantation. It is difficult to assess the overall benefit of changing paradigms years in advance of reported outcomes, with all of these other factors playing a role. So we have to make our decisions based on the data available today and the benefits we know that exist between one drug and another.

**KOGAN:** If we can anticipate the full range of associated pieces of the therapy, we may be able to make more longitudinal decisions. We would need to know relative efficacy, potential AEs and their treatments, the cost of each, and how many cycles are required, as well as the parameters to determine when to start treatment, what defines a nonresponse, and how soon can you identify that. In other words, a complete package of care.

**DUNN:** It is very attractive to prefer one agent over another, but it must be accomplished by collaboration. You must sit down with the physicians who actually treat patients and see the outcomes and say, “Here’s the data on comparative effectiveness and the evidence on survival, toxicities, site administration, and subsequent hospitalization. We think the survival data favors one product, which will potentially cost less due to outpatient delivery, and it is associated with fewer hospitalizations for AEs.” Then, as a team you can make the decision to document a preferred regimen.

**FRAME:** The survival advantage with azacitidine is real, and a similar benefit has not been shown with decitabine in the same population. The studies being done with alternative schedules are confounded by details like enrollment of patients predominantly with earlier disease, and the failure to include the approved regimen as a comparator. So for now, I think the survival advantage and outpatient delivery with the traditional azacitidine schedule in patients with higher-risk disease may be the key factors in selecting a preferred therapy for these patients.
The Role of Specialty Pharmacy in the Treatment of Myelodysplastic Syndromes

KIRBY ENG, RPh
Director, Oncology Management Services, CVS Caremark

KEY POINTS

- Specialty Pharmacy provides unique and dedicated services to optimally manage high-cost specialty pharmaceuticals and biologics.
- Medication access, adherence to complex dosing regimens, and patient education are critical areas where Specialty Pharmacy can provide supportive services to optimize patient outcomes and satisfaction.
- Specialty Pharmacy can assist with MDS treatment programs to better manage the financial challenges posed to patients, providers, and payers.

Specialty Pharmacy has emerged as a means to manage the delivery of, improve access to, and address the challenges posed to patients, physicians, payers, and pharmacies by the newer pharmaceutical and biologic products. These products often come with high acquisition costs, challenging regimens, and difficult reimbursement patterns. Many of the medications used in the treatment of myelodysplastic syndromes (MDS) — e.g., lenalidomide, azacitidine, decitabine, and the supportive care drugs erythropoietin, darbepoetin, filgrastim, sargramostim, pegfilgrastim, and deferasirox — fall under the Specialty Pharmacy umbrella. Thus, Specialty Pharmacy can assist with MDS treatment programs to optimize patient outcomes and satisfaction and help manage the financial challenges for the patient, healthcare provider, and payer.

Where the challenges lie

A number of factors influence the success of treatments for MDS. Although many of the medications have proven effective in slowing the progression of or improving the hematologic profile of MDS, there are features of these medications and their regimens that challenge their optimal use. As a result, Specialty Pharmacy has become a purveyor of unique and dedicated services designed to help ensure favorable outcomes in the face of access challenges, complex dosing regimens, the need for patient education, inpatient versus outpatient treatment options, requirements for ancillary or supportive therapies, and rising medication costs (Hay 2008).

Specialty pharmaceuticals such as those prescribed for MDS can be quite costly (Goss 2006, Greenberg 2008, Sullivan 2008), and the financial demands associated with these agents place a great burden on patients that potentially can impede access to effective treatment. They can also impose a strain on patients’ families and their employers and managed care providers. Employers and third-party payers must deal not only with the direct costs of health care coverage, but also with the indirect costs incurred in effectively treating patients with a life-threatening disease. Health care providers must address the demands of complicated and time-consuming regimens and understand the managed care considerations for those treatments. For example, eligibility and benefit verification is a vital step in treatment planning, because easy access to therapy depends on identifying the unique parameters of each patient’s benefit plan prior to assigning a therapy program.

Cost-plus-benefit is the factor in defining a preferred treatment regimen. Several trials have established that hypomethylating therapies can effectively treat MDS (Fenaux 2009, Steensma 2009, Wijermans 2008, Wilson 2007), but few well-designed economic analyses have evaluated the cost-plus-benefit of patient outcomes versus treatment-associated costs. The few relevant pharmaco-economic studies available (Radaelli 2004) suggest that the key drivers of cost in the treatment of MDS and its potential progression to acute myeloid leukemia (AML) are hos-
pitalization, length of stay for initial therapy, and the need for transfusion. Peripheral blood stem cell transplants also contribute to cost, but relatively few patients are eligible for this treatment. It has been shown, however, that when used in an appropriately targeted population, the approved pharmacologic agents can improve the hematologic profile of MDS, reverse transfusion dependence, and, in some cases, prolong survival, suggesting substantial benefit to offset costs (Fenaux 2009, Sullivan 2008, Wijermans 2008, Wilson 2007).

With the availability of new effective medications comes the likelihood that, like other cancers with remission-inducing therapies, pharmacologic therapy for MDS may become a chronic rather than an acute event (Cook 2008). In advanced MDS, treatment with the hypomethylating agent azacitidine has prolonged survival to 24 months compared to 15 months with conventional care regiments ($P=.001$) (Fenaux 2009). Furthermore, specific data suggest that patients with MDS may benefit from long-term maintenance therapy, as response to traditional induction therapies, such as ara-C and anthracycline, are generally of limited duration, and maintenance treatment with, for example, hypomethylating agents has been shown to extend treatment response (Grövdal 2008).

Side effects, too, contribute to the demands of MDS therapies. As a result, a great deal of effort in the form of patient education, risk evaluation and mitigation strategies, and supportive interventions are required to reduce the impact of medication toxicities. Complex dosing schedules, significant toxicities, and potential drug interactions also interfere with patient adherence to therapy.

**Meeting the challenges**

CVS Caremark provides unique services to assist providers and health care plans in delivering the best patient care and in optimally managing specialty pharmaceuticals (Sullivan 2008). These services can be categorized as separate yet interrelated functions: customer service, utilization management, patient care management, and cost management.

**Customer service.** At CVS Caremark, customer service is primarily a function of benefit and eligibility verification. When a patient gets a prescription for a medication, he or she is given a telephone number to call to speak with a front-end client services agent at the Specialty Pharmacy. This representative, upon determining the patient’s carrier and benefits, will ascertain eligibility, verify specific benefits, communicate any patient financial responsibilities, and collaborate with the patient’s physician and health plan to secure any required authorization for treatment.

**Oncology utilization management.** To establish standards of care and to help promote global clinical practices, particularly with specialty pharmaceuticals like those used in the treatment of MDS, CVS Caremark has a designated clinical team that reviews national guidelines, recent literature, and reported outcomes associated with current standards of care to develop, update, and administer standardized practice criteria. The criteria that CVS Caremark uses for prior authorization are based on two primary drivers: Whether the drug as prescribed is appropriate for the intended use, and whether there are safety concerns associated with that drug for the indication prescribed. CVS Caremark also can provide patient assessments to monitor adherence to prescribed regimens. In this capacity, the pharmacist is charged with more frequent interaction with the patient to assess top-line treatment response, determine need for re-education and encouragement, and promote strategies to improve treatment success.

**Patient care management.** At CVS Caremark, after a front-end customer services representative has clarified the patient’s coverage and benefits status, the patient is assigned to a Patient Care Team consisting of trained pharmacists, nurses, and patient service representatives that are usually certified pharmacy technicians. The Care Team reviews with the patient the specific features of his or her benefit design as it affects the diagnosis, clarifying what treatment measures are covered and whether there is a coordination of benefits and other unique service needs based on the treatment and condition of the patient. The Care Team strives to build a one-on-one continuing relationship with each patient to ensure patient education, effective and safe medication use, prescription fulfillment, and financial considerations that can impede access to medication (Table). The pharmacist on the Care Team is responsible for confirming dose accuracy, minimizing or eliminating potential drug interactions, and coordinating medication shipments. Because many patients who are diagnosed with an oncologic condi-

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**TABLE**

**Specialty pharmacy services for MDS patients**

- Customer services (various)
- Prescription fulfillment
- Dose accuracy
- Drug interactions
- Shipment coordination
- Drug education
- Adherence to treatment regimen
- Financial assistance programs
- 24/7 pharmacist availability
- Dedicated oncology teams

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**Disclosure:** Kirby Eng, RPh, states that he does not have any financial arrangements or affiliations that might constitute a conflict of interest with this article.
tion experience much anxiety, the continuing relationship with a patient service representative can offer emotional support as well.

For newly diagnosed MDS patients, the Care Team offers education about MDS, prescribed medications, and lifestyle issues and also recommends strategies to ensure medication compliance. The Care Team also performs regular follow-ups, calling patients as often as needed to check progress and proactively coordinate medication refills and supplies. In the event of financial challenges, a dedicated team will help a patient with reimbursements, copayments, benefits clarification, and manufacturer assistance programs. Pharmacists are available to patients 24/7 to answer questions about treatments and their side effects.

Cost management. Because there are a limited number of drug agents used to treat MDS, Specialty Pharmacy is currently limited in its ability to negotiate drug discounts as with some other therapies. However, Specialty Pharmacy can help manage MDS drug costs by ensuring its appropriate use in accordance with U.S. Food and Drug Administration-approved indications or nationally recognized evidenced-based treatment guidelines and monitoring the safety of prescribed pharmaceuticals, e.g., ensuring dosing accuracy and identifying potential drug interactions or side effects, which allows the patient or prescribing physician to take preventive or corrective measures as necessary.

Future trends

Specialty Pharmacy is a growing segment of the healthcare industry, and its involvement with oncology medications is on the rise. As a result, the focus of future efforts must take into account the need to keep pace with this growth, including maintaining a knowledge base of the increasing numbers of approved medications and combination regimens, supporting adherence as medication options and regimens increase, continuing to monitor research and modify guidelines accordingly to ensure best outcomes, and overseeing cost-effective drug utilization by defining formularies and step-therapy approaches. Specialty Pharmacy is also uniquely positioned to effectively manage FDA-mandated risk evaluation and mitigation (REMS) programs. As the number of oncology drug-required REMS programs increase, we will also see some standardization in the requirements allowing program objectives to be met cost-effectively.

Summary

Specialty Pharmacy plays an integral role in the delivery and management of biologic and chemotherapeutic medications for patients with higher-risk MDS by streamlining the delivery process, educating patients, monitoring treatment adherence and response, managing complex storage and delivery requirements, and assisting both patients and payers with clinical, operational, and financial issues and challenges. Specialty Pharmacy will continue to develop procedures to assist clinicians and patients, maximizing access to pharmacy and clinical advisors who are able to explain medical diagnoses to patients, walk them through medication options, and describe the specific details of therapeutic regimens. Where the use of specialty pharmaceuticals poses challenges of inventory, sourcing, complex treatment regimens, patient adherence, and slow reimbursement, Specialty Pharmacy has designed standardized processes to address these needs and will continue to improve and increases its services to support vital business and clinical functions for patients, health care plans, and providers.

References

DISCUSSION

STEVEN R. PESKIN, MD: Mr. Eng, you mentioned that CVS Caremark is one of the largest dispensers of oral oncology drugs in the United States. Have you seen an increasing role for Specialty Pharmacy in the infusion/injection drug area?

KIRBY ENG, RPh: Yes. While we have seen a significant number of new oral oncology drugs come to market, the majority of oncology drug spend still consists of infused/injected drugs, typically administered in a physician’s office and covered under a medical benefit design. Recent national payer surveys have indicated that payers are willing to adopt more aggressive oral oncology drug management strategies and will continue to explore infusion/injectable drug management options, including Specialty Pharmacy.

JEFFREY D. DUNN, PHARMD: As part of a health care system, we have most of the patient functions that Kirby described in-house, but we do use a Specialty Pharmacy for distribution.

ALLAN JAY KOGAN, MD: In certain categories like oncology, we do not have a large enough market to leverage the costs of some of these oncology drugs and would need to have a liaison program with a Specialty Pharmacy. Kirby mentioned the growing role of CVS Caremark in the oncology space, and we might use those patient care and medication oversight services as well. Our providers would come up with the proper diagnosis and assign a treatment regimen, but then they might capitate it to the Specialty Pharmacy and allow them to oversee the long-term servicing of patient follow-up and medication management.

PESKIN: As we move away from oral medications for MDS to injectable and infusional therapy, does it make sense to work more closely with Specialty Pharmacy? Or are these treatments going to end up in the oncologist’s office?

ENG: For the foreseeable future, infused/injective oncology drugs will likely continue to be administered in an oncologist/hematologist office under the physician buy-and-bill model. Specialty Pharmacy will come into play if it can transition proven oral oncology drug management strategies into infused/injective drug formulations.

KOGAN: And as regimens move into a stacking mode—that is “If A and B work, why don’t we use them together?”—the paradigm gets even more complicated. Cost and regimen safety become even more compelling goals. That is why there has become a focus on specificity in treatment and personalized medicine. We need to know we are treating people with regimens to which they will respond and still aim to minimize toxicity. As a payer, our business is risk management. We are interested in prolonged survival and improved quality of life, but also in what are the associated costs of that improvement? Not just the drug treatment costs, but the total expenditures, including costs of managing adverse events and use of adjuvant therapies to reduce risk or prevent complications.

DAVID FRAME, PHARMD: That is what was interesting about the hypomethylating agent studies of Fenaux [2009] and Steensma [2009a,b], because that’s the only data I know of that looks at a snapshot of MDS patients at any given time. Only 13 percent of patients treated with azacitidine were hospitalized. In the study with the revised decitabine regimen, 65 percent of patients were admitted to the hospital due to side effects. Those were truly notable findings.

PESKIN: What is the role of academic physicians in sorting out guidelines that might influence reimbursement, influence access, and simplify payments—that intersection of clinical practice and economics?

BART L. SCOTT, MD: Historically, physicians have been reluctant to involve themselves in that discussion because of potential conflict of interest between patient care and economics. But one of the things that we can do is to design better clinical trials, where we do look at adverse events and at the overall cost of care, and of course make better use of evidence-based medicine. It is important to remember that we all want the same thing and that is good patient outcomes at reasonable cost.
the off-label use of approved medications has become a widespread strategy for expanding the usefulness of novel medicines. With the generally high costs of these products, health plans must devise new strategies to ensure that quality care, positive outcomes, and patient safety remain the goals of treatment for all patients while continuing to maintain a rational focus on cost control mechanisms.

**Changing treatment paradigms**

Progress in therapeutic interventions often is achieved by changing the treatment paradigm. For example, an advance in treatment delivery may be based on improving the mode of administration for increased efficacy, convenience, and safety. This is evident in the case of two hy-

### KEY POINTS

- New, effective therapies for MDS have led to earlier initiation of treatment and prolonged survival.
- Health plans must devise strategies that not only ensure quality patient care and positive outcomes but also maintain a rational focus on cost control.
- Active collaboration among health care providers, patients, and health plans is essential to improve the efficient management of MDS patients and improve the overall health care economy.

The use of specialty oncology products poses a number of challenges to all stakeholders involved in managed care medicine — patient, provider, employer, and health plan. Issues of cost, delivery method, dosage, length of treatment, benefits design, and approved versus experimental use of medications are among the variables that complicate the health care system and threaten the cost-effective administration of novel oncologic therapies. The increasing availability of effective targeted therapies for myelodysplastic syndromes (MDS), which have a relatively low incidence and prevalence compared with other cancers, has led to earlier initiation of treatment and prolonged survival. This trend means more medication delivered over longer periods, inciting a growing concern about how health plans can efficiently cover the cost of these treatments.

The need for long-term or maintenance therapy in MDS can transform the challenges of cost of care further. Maintenance regimens prolong therapy and may necessitate altered dosages or increased dosing frequency, demanding changes in the standard of care, increased provider education, and updated health benefits programs. Once the activity of newer agents is established for one oncologic indication, it has become standard that they are investigated for other diagnoses. Furthermore,
pomethylating agents for MDS — decitabine (Dacogen), an intravenous (IV) infusion that has an associated need for clinic or hospital admission, high resource utilization, and greater risk for complications, and azacitidine (Vidaza), a subcutaneous (SC) injection or IV infusion that has a simplified administration protocol and a few inexpensive add-ons.

Similarly, advances in pharmacologic intervention for cancer are frequently attempted by combining therapies. Rather than switching from one medication that yields only short-term or partial responses to another medication in an attempt to achieve a better outcome, which is the basis for the sequenced or step-therapy approach, oncology treatments are more likely to be “stacked,” that is added one on top of the other. Theoretically, the goal of this approach is to improve outcomes by combining complementary drug mechanisms from proven active products to drive up the response. But there is a cost involved in this approach, and not just the cost associated with prescribing multiple medications. Personalized medicine is lost, so that many patients who do not benefit are treated with a predefined combination regimen that realizes an improved outcome for only a few individuals. There is the potential for increased toxicity with a multidrug regimen and the resultant need for supportive therapies to minimize or manage adverse events. In addition, there might be different schedules and doses for the multiple agents, which can complicate the delivery of the regimen, necessitating greater clinic or provider time, less convenient schedules for the patient, and an increased risk of nonadherence. Can a health plan provide maximum benefit from this approach while managing risk and controlling costs?

**High cost of medications**

It is becoming increasingly expensive to develop a drug and get it to market, and the cost is invariably passed on to the consumer. Drugs are being developed that carry higher and higher ticket prices, which can be compounded by different features of the prescribed regimen. The cost per course is one way to compare the economics of treatments, but it is not the bottom line. The course schedule, e.g., every 6 weeks or every 8 weeks, and the length of therapy contribute to the final financial expenditure. Some prescribed treatments are based on body mass or laboratory markers, which makes for variable pricing related to unique patient characteristics. In addition, preventive interventions and management of adverse events must be added to the bottom line, and the potential benefits of long-term maintenance therapy can increase costs exponentially. Waste also must be considered — if only a half-vial of medication is used, the lost portion of the pre-packaged product must be factored into the final cost of treatment.

A top-line comparison of treatment costs associated with the FDA-approved dosing of decitabine versus azacitidine for 6 months of therapy administered subcutaneously, as reported by the drug information database MediSpan, is shown in the accompanying Figure. Using the U.S. Food and Drug Administration-approved dosing regimen for each medication, this analysis suggests that the expected expenditures for drug administration alone is $62,145 for decitabine, based on a 15-mg IV infusion given every 8 hours for 3 consecutive days and then repeated every 6 weeks compared with $48,989 for azacitidine given as a 75mg/m² SC injection for 7 consecutive days, repeated every 4 weeks. Clearly, both are expensive treatments, although decitabine costs are about 25 percent greater. Yet, these estimates do not take into account the ancillary expenses for hospitalizations, erythropoiesis stimulating agents, management of side effects, or physician visits — expenses that could potentially double the regimen costs. If, indeed, the use of maintenance regimens to prolong response to therapy becomes standard in the treatment of MDS, these numbers will rise even further. Cost, regimen, tolerability, and schedule are contributing to a challenging environment in which payer organizations must develop benefits programs that best assign increasingly limited resources to cost-effective and evidence-based protocols.

**Economic considerations**

The struggles of the current economy have added new challenges to the benefits coverage quandary. There has been a rise in unemployment and, thus, a contraction in

<table>
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<th>Drug</th>
<th>Dose*</th>
<th>AWP $/day/course</th>
<th>AWP $/month or cycle</th>
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<td>decitabine</td>
<td>15 mg/m² every 8 hours x 3 days, then every 6 weeks</td>
<td>50 mg vial = $1726 x 3 vials x 3 days = $15,535 (assumes 1 vial/dose)</td>
<td>$15,536.25 x 4 = $62,145</td>
</tr>
<tr>
<td>azacitidine</td>
<td>75 mg/m² every day x 7 days, then every 4 weeks</td>
<td>100 mg vial x 2 vials = $1,166 x 7 days = $8,164.94 (assumes 2 vials/dose)</td>
<td>$8,164.94 x 6 = $48,989</td>
</tr>
</tbody>
</table>

*All doses may require adjustment based on tolerability, lab values, etc. Source: MediSpan
health plan membership. Despite an increase in the number of groups enrolled at SelectHealth, for instance, individual memberships have gone down, thus putting a greater burden on available resources.

Changes in benefit design are at a critical point in balancing payer versus patient expenses for covering health care. With co-insurance plans, patients are paying more of the cost of their treatments. Assigning drugs to formulary tiers can reduce costs to the payers, especially with higher-tier drugs for which patients pay an increasing part of the cost. But increasing patient share can limit access to medicines or impede the full and proper use of therapy, reducing compliance, impairing efficacy, and ultimately increasing overall costs. In the current economy, patients are unable to meet their financial obligations under their health benefits design. On the other hand, attempting to revise the design to improve benefits for patients is an expensive endeavor. Re-establishing costs and defining new best practices involves the work of a team of managed care consultants, including actuaries, marketers, clinicians, and government liaisons among others.

Clinical issues
Several clinical factors influence managed care decisions for MDS patients. Research support and documented evidence of efficacy and safety are considered in best practices guidelines and coverage paradigms. The National Comprehensive Cancer Network clinical practice guidelines (NCCN 2009), which provide treatment algorithms and are regularly updated to reflect ongoing research and changing evidence, should certainly be considered. In a very delicate ethical analysis, details of prognosis, survival, palliation, and quality of life (QoL) must be balanced against the costs of treatment to determine the value proposition of a regimen. Anticipated outcomes are part of the equation as well, with questions of survival, toxicity, and QoL also playing a role in treatment guidelines and benefits decisions.

Provider relations with payer organizations also influence the overall design of a health care plan. Negotiated fee schedules and reimbursement parameters must satisfy both parties. Place of therapy and right of administration, i.e., clinicians’ preference to administer medications themselves, are factors in the decision-making process. In addition, local network issues such as defined fees and comparative incentives from different networks can determine how providers in the community interface with local health plan organizations.

Potential strategies to improve care and control costs
A number of strategies are currently under consideration aimed at improving current benefits designs (Table), from cost shifting to altered tiering structures and better case management to improved guidelines and treatment algorithms. The challenge is in finding the best strategy right out of the gate. How do we determine the proper mix of tiering and patient expense? Will the concept of two-tiered medical benefits be accepted? How can case managers provide better services in the oncology arena?

To minimize their outlay, employers are shifting costs to place more responsibility on employees for their health care. Some businesses are encouraging their employees to participate in health savings accounts, tax-sheltered accounts in which individuals can accumulate pre-tax dollars to pay for the deductible portion of their insurance coverage (Hall 2005, Robinson 2005). They are also more likely to offer insurance policies with a co-insurance provision, meaning the insured is required to pay a percentage of expenses after the deductible has been met up to the policy’s stop-loss provision. Only after the insured’s payout equals the stop-loss, does the insurer provide 100 percent coverage. But these approaches can overburden patients. If patients cannot afford their cost share, they may discontinue treatment, leading to loss of medication efficacy and treatment failure, which subsequently drives up the overall cost of patient care.

Increased formulary control with prior authorization requirements, dose optimization, step therapy, and net effective pricing are all mechanisms being used by health plans. Mandatory patient support programs can improve outcomes and lay the groundwork for educated decision making when the need for treatment adjustment

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<td><strong>Potential strategies</strong></td>
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| • Benefit design  
  - Tiers, evaluating out-of-pocket expenses and distribution  
  - Biosimilars  
• Better case management  
• Guidelines/algorithms/disease management  
  - “More than just NCCN”  
• More formulary control  
  - Data  
  - Contracts  
  - Work with pharma – Outcome based  
  - Net effective pricing  
  - Mandatory patient support programs  
  - Prior Authorizations – levels of evidence, quantity limits  
• Incentive programs  
  - Member  
  - Physician – differential reimbursement, Pay For Performance  
  - Is oncology a “value-based” disease state?  
• Specialty Pharmacy  
• Fee schedules  
• Coordination/collaboration  
• Electronic records (IT) will be key |
arises. A larger role for the specialty pharmacy may also smooth the way to better patient management. The safe and effective use of new medications and fee schedule optimization to satisfy all stakeholders will help to improve the overall economy of the health care field.

It also is important to consider all the factors that influence the usage of medication by a patient. For example, although an oral medication may be preferred by a patient over an injectable or infusible medication, non-compliance is a major issue, because oral agents are not taken under a clinician’s supervision. Also, the overall cost of therapy can determine whether a patient follows through with treatment. In MDS, for example, the final cost of treatment with decitabine varies, based on body mass, and includes 3 days of infusion therapy per course. The total cost has been estimated at $62,145 for the four recommended courses, exclusive of hospitalization costs. On the other hand, the cost for four recommended courses of azacitidine, a SC injection, is estimated to be about $49,000. Although both costs are high, the relatively lower cost of azacitidine and the lack of hospitalization requirement may mean that patients are more likely to maintain the regimen.

Providers also must consider the overall clinical benefit of treatment. Because azacitidine has been shown to improve overall survival in patients with higher-risk MDS, whereas decitabine has not, the choice should fall in favor of the treatment with the more favorable clinical outcome. To summarize, the preferred treatment should be selected based on potential for adherence, better cost management, and best clinical outcome.

Most importantly, collaboration and shared data are key factors in optimal best care practices. An up-to-date database of a patient’s history, diagnosis, laboratory values, and prior treatments should be available to all parties involved in a patient’s care. Without integrated systems, health care decision making is impaired. Cooperation on formulary development may be another important step to improving the current paradigm for oncology. If the payers and pharmaceutical companies can agree on formulary preferences and make them available at reduced costs, all stakeholders may benefit in the long run. Incentive programs, e.g., higher reimbursements for physicians or lower premiums for members who adhere to prescribed protocols, has been effective in other therapeutic areas and should be considered in oncology as well. If oncology is a value-based disease state, is there value in offering a medication like azacitidine at a lower benefit level? Is there a return on investment by ensuring that patients are treated with a preferred medication?

Overall, there needs to be better collaboration among the health care provider, the payer or health plan, and the patient with a focus on optimal response, cost management, and patient satisfaction to ensure everybody wins.

Summary

Costs associated with treating cancers such as MDS are increasing as new medicines are developed and combination regimens gain hold. This trend presents an important challenge to MCOs who must respond to changing protocols and rising costs. Whereas the new oncology medications offer a unique opportunity to improve outcomes in patients with MDS, they also demand high financial outlay, which in turn necessitates adjustments in benefits programs. As payers look to manage expenses in ways that satisfy all stakeholders, increasing importance is placed on scientific evidence, survival and QoL benefits, tolerability factors, and evidence-based standards of care. In the treatment of higher-risk MDS, this means weighing those differences between the two hypomethylating agents approved for this indication — azacitidine and decitabine — in terms of proven effectiveness, safe delivery, and survival gains validated in clinical trials as well as potentially reduced costs related to administration method and fewer treatment-related toxicities.

The future of MDS treatment in the managed care setting will require complex decision making to determine new treatment guidelines, benefit design, reimbursement plans, ethical considerations, and formulary development. Economic and clinical strategies must aim to make optimal use of novel treatment approaches while meeting the financial objectives of MCOs. The goal is improved patient outcomes at reasonable cost, a challenge that will be addressed only with continued discussion and study. The therapies azacitidine and decitabine may offer a good model for decision making to drive best treatment for MDS while moderating cost.

References


DISCUSSION

STEVEN R. PESKIN, MD: We have talked about the need for guidelines to standardize care in the oncology area. Where are we on that now?

BART L. SCOTT, MD: The guidelines we rely on now are those developed by the National Comprehensive Cancer Network (NCCN). But those guidelines, although
a useful mechanism to give some structure to an otherwise chaotic field, are confusing to some clinicians and, therefore, have limited utility as a national standard of care. Some organizations have suggested they will be working on more practical alternatives.

KIRBY ENG, RPh: Organizations, such as the University of Pittsburgh Medical Center, US Oncology, and others, have also created oncology drug treatment guidelines or pathways. All have purported advantages and disadvantages, and the question is whether they help or further confuse identifying treatment options that produce optimal clinical and financial outcomes.

ALLAN JAY KOGAN, MD: If, as intended, any new guidelines are evidence-based, clinically relevant, and responsive to the latest data in real time, they could be very beneficial, especially if a group like US Oncology, which is very influential in the oncology arena, drives the change.

DAVID FRAME, PHARMD: I agree. The goal is to achieve a higher evidence base. Although the NCCN is pretty good at updating their guidelines, there is room for improvement in adapting state-of-the-art data to real-time data.

PESKIN: What have been the most important changes you have observed in the diagnosis and management of MDS?

FRAME: From an internal medicine perspective, we’ve seen an increase in diagnosis now that there are therapies that are effective in treating this disease. Practicing internists in the Detroit suburbs or Kalamazoo are actually more aware of MDS and are making the diagnosis more often and earlier. More patients are being referred to the community oncologist. But that means patients are showing up at the academic centers with more refractory disease.

KOGAN: The whole oncology space has shifted dramatically with the ongoing development of new drugs to treat these stage III and IV cancers. Although the benefits can be dramatic, most patients realize only a 2- or 3-month survival prolongation. It is a very expensive area, so we must continue to weigh the value proposition in terms of the cost versus outcomes. But with many drugs in the pipeline, this analysis is an ever-changing target. The key issue is that we do not want to pay for anything experimental, so we’re absolutely committed to adhering to NCCN guidelines.

SCOTT: The emergence of these new treatments has definitely changed referral patterns, so we tend to see patients with more advanced diseases that have failed prior therapy. My concern, however, is that frequently the duration of therapy is not long enough and many patients are discontinued from treatment and either do not achieve an adequate response or recur rapidly.

PESKIN: In establishing an accurate diagnosis, do you require evidence that a bone marrow analysis was done?

KOGAN: We have a clinical oversight program in quality oncology, a formalized review system carried out by active oncologists, some of whom are on our internal teams but others are specialists from outside organizations. We have a checklist that they address, from bone marrow analysis to prior authorization, for drug use and approval of supportive care therapies like ESAs.

JEFFREY D. DUNN, PHARMD: Pharmacy manages the PAs, but we basically rely on the oncologist’s diagnosis and do not monitor for bone marrow aspirates.

PESKIN: How are issues of access and patient cost burden affecting the general health care environment?

ENG: An emerging challenge is the function of drug benefit design and the out-of-pocket patient costs for oncology drugs. Given the high costs of many of the newer agents, patient access may be affected. A number of states are looking at legislation that will require that patient financial obligations for these and other drugs be the same regardless of the drug benefit design.

DUNN: The focus of our attention these days is drug utilization, i.e., how often is a drug used, what are the indications, are there many off-label requests? If we don’t get a handle on these issues, sooner or later we’re going to run out of money. Employers are looking for ways to shift their costs. So for infusional drugs, with co-insurance, you’re talking about 25 to 50 percent of the cost, which can be $2,500 to $5,000. We’re probably 3 or 4 years behind where we should be in figuring out how to resolve these issues.

FRAME: From a hospital perspective, our numbers of uninsured or underinsured have gone up dramatically. In 1 year, it has affected our bottom line more than ever before, and for the first time, we’ve actually had layoffs. When I arrived at the University of Michigan 4 years ago, we didn’t do PAs for most cancer agents. Now PAs are in full effect. Many of our decisions on what to give patients are based on what they can pay.

PESKIN: Given the evidence that we heard regarding survival data, treatment efficacy, delivery methods, and adverse events, how should MDS best be managed?

DUNN: From a cost perspective, it makes sense to start managing MDS in its earliest stages, when the disease state is less aggressive.

KOGAN: I think we definitely have to work out an algorithm for this condition. With data support or not, we need an approach that is transferable across different populations and across different health systems.

PESKIN: Dr. Dunn, can you summarize the messages in your presentation?

DUNN: I hope that Dr. Kogan and I were able to effectively convey the challenges that health plans face in delivering integrated financing for the health care environment. We need to keep up with the needs of an ever-changing health care system to create a medical environment that meets the needs of all Americans.