March 2008 www.clinicaladvances.com Volume 6, Issue 3, Supplement 6

Advances in the Treatment of Myelodysplastic Syndromes

A Review of Selected Presentations
From the 49th American Society of Hematology
Annual Meeting and Exposition
December 8–11, 2007
Atlanta, Georgia

With expert commentary by:
Guillermo Garcia-Manero, MD
Associate Professor of Medicine
Chief, Section of Myelodysplastic Syndromes
Department of Leukemia
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas

A CME Activity
Approved for 1.0
AMA PRA
Category 1 Credit(s)™

Release date: March 2008
Expiration date: March 31, 2009
Estimated time to complete activity: 1.5 hours

Supported by an educational grant
from Pharmion Corporation.

Sponsored by Postgraduate Institute of Medicine.

Clinical Advances in HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Included in Index Medicus/PubMed/Medline

Disclaimer

Funding for this Conference Presentations Review has been provided through an educational grant from Pharmion Corporation. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporters, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

Release date: March 2008
Expiration date: March 31, 2009
Estimated time to complete activity: 1.5 hour

Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in the management of patients with myelodysplastic syndromes (MDS).

Statement of Need/Program Overview:

In this time of accelerated development of new and effective treatments for MDS, it is imperative that clinicians treating patients with MDS have the latest information in order to achieve improved patient outcomes.

Educational Objectives

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

- Discuss findings from studies presented at ASH 2007 on the treatment of MDS.
- Review the results of these new study findings, including clinical trials evaluating new treatment options in MDS.
- Select the latest knowledge and methods for treating patients with MDS with newly available options related to applicability to clinical practice.
- Identify future research directions for the treatment of MDS.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Millennium Medical Publishing. PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: Postgraduate Institute for Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest: Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Disclosures:

Guillermo Garcia-Manero, MD, has received consulting fees from Pharmion Corporation and MGI PHARMA, Inc., as well as funding for research from Pharmion Corporation, MGI PHARMA, Inc., and Merck.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Jessica Wapner: No real or apparent conflicts of interest to report.
Jan Hixon, RN: No real or apparent conflicts of interest to report.
Lisa M. Cockrell: No real or apparent conflicts of interest to report.

Method of Participation: There are no fees for participating and receiving CME credit for this activity. During the period March 2008, through March 31, 2009, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 70% or better. Your statement of credit will be mailed to you within three weeks.

Media: Monograph

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Postgraduate Institute for Medicine (PIM), Millennium Medical Publishing, and Pharmion Corporation do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Millennium, and Pharmion Corporation. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Introduction

Myelodysplastic syndromes (MDS) refer to a number of clonal disorders that occur in hematopoietic progenitor cells. The current understanding of the disease pathology is that it arises through numerous pathways, as evidenced by the widely varied clinical courses of the various MDS subtypes.[1] Because the disease arises in the hematopoietic progenitor cells, patients experience ineffective hematopoiesis, leading to clinical manifestations such as anemia, neutropenia, and thrombocytopenia.[2] Common disease-related complications arising from MDS include transfusion-dependent anemia and increased risks of hemorrhage and infection. Additionally, approximately 30% of MDS patients progress to acute myelogenous leukemia (AML), a difficult-to- treat and potentially life-threatening malignancy.[3]

The annual incidence of MDS is 2–12 cases per 100,000 individuals; however, the incidence increases up to 50 cases per 100,000 for individuals 70 years and older.[4] Increased life expectancy, combined with improved awareness and diagnosis among clinicians, has led to a growing prevalence of MDS. The association of increasing risk for MDS in aging patients has led to one model of disease initiation whereby genetic damage accrued over time causes hematopoietic progenitor cell transformation.[5] However, although nearly half of all MDS patients exhibit cytogenetic abnormalities, the function of these abnormalities in disease pathology is not well understood. Aside from age, other risk factors for the development of MDS include prior chemotherapy treatment, immunosuppression, smoking, and exposure to radiation, diesel fuel, or solvents such as benzene.[5] Accordingly, MDS can arise de novo or secondary to one of these risk factors.

MDS can be categorized according to several classification systems.[6] The French-American-British (FAB) system bases classification on bone marrow morphology and contains five MDS subgroups: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RA with excess blasts in transformation to leukemia (RAEB-T), and chronic myelomonocytic leukemia (CMML).[7] However, several biochemical and molecular advances in the understanding of MDS have occurred subsequent to the development of the FAB system. In 1997, the World Health Organization (WHO) developed a new classification system. The most important difference between the WHO and FAB classifications was the lowering of the blast threshold for the diagnosis of AML from 30% to 20% (also thereby eliminating the FAB category RAEB-T). Other changes included the addition of a new category, refractory cytopenia with multilineage dysplasia (RCMD); subdividing RAEB according to percent marrow blasts; defining 5q- syndrome as a unique MDS subtype; and removing the CMML subgroup.[8]

At approximately the same time, the International Prognostic Scoring System (IPSS) was developed as a method for evaluating prognosis in MDS.[9] The IPSS incorporates the number of peripheral cytopenias, percentage of bone marrow blasts, and chromosomal abnormalities and assigns a score to predict survival and risk of disease progression to AML. The IPSS classifies patient risk as low, intermediate-1, intermediate-2, or high. The most commonly occurring cytogenetic abnormality in MDS is deletion of chromosome 5q.[10] Although patients with a chromosome 5q deletion as the sole karyotypic abnormality have a relatively good prognosis, del(5q) plus additional cytogenetic abnormalities is associated with a poorer prognosis and increased risk of transformation to AML. Other chromosomal abnormalities include, for example, translocation at 11q23, trisomy 8, inversion or deletion of chromosomal region 3q, and deletions of the chromosomal regions 7, 20q, or 17p.[9]

Treating Patients with Myelodysplastic Syndromes

The IPSS has become widely used to stratify patients for MDS therapy.[11] Generally, patients with low-risk MDS are not considered candidates for intensive therapy. When considering intensive therapy for higher-risk individuals, several factors should be discussed with the patient. Hematopoietic stem cell transplantation carries with it a high risk of transplant-related morbidity and mortality.

And although combination chemotherapy regimens can restore normal hematopoiesis in up to 50% of patients, relapse is a frequent and problematic occurrence.

Advances in the knowledge of MDS and AML disease pathogenesis and progression have allowed the introduction of several new therapies in recent years. Azacitidine and decitabine are two agents classified as demethylation or hypomethylation agents.[12-14] These drugs reduce the amount of methylation present on certain regions of the DNA, where it normally acts to repress genes important for the regulation of normal cellular function.[15] Another new drug option for these patients is lenalidomide, a derivative of thalidomide.[16] Although the mechanism of action of lenalidomide in MDS has not been clearly established, it may work by immunomodulation.

References

1. Warlick ED, Smith BD. Myelodysplastic syndromes: review of pathophysiology and current novel treatment approaches. *Curr Cancer Drug Targets.* 2007;7:541-558.
2. Catenacci DV, Schiller GJ. Myelodysplastic syndromes: a comprehensive review. *Blood Rev.* 2005;19:301-319.
3. Disperati P, Ichim CV, Tkachuk D, et al. Progression of myelodysplasia to acute lymphoblastic leukaemia: implications for disease biology. *Leuk Res*. 2006;30:233-239.
4. Aul C, Giagounidis A, Germing U. Epidemiological features of myelodysplastic syndromes: results from regional cancer surveys and hospital-based statistics. *Int J Hematol*. 2001;73:405-410.
5. Corey SJ, Minden MD, Barber DL, et al. Myelodysplastic syndromes: the complexity of stem-cell diseases. *Nat Rev Cancer.* 2007;7:118-129.
6. Bennett JM, Komrokji RS. The myelodysplastic syndromes: diagnosis, molecular biology and risk assessment. *Hematology.* 2005;10(suppl 1):258-269.
7. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982;51:189-199.
8. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* 2002;100:2292-2302.
9. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89:2079-2088.
10. Mihara K, Takihara Y, Kimura A. Genetic and epigenetic alterations in myelodysplastic syndrome. *Cytogenet Genome Res.* 2007;118(2-4):297-303.
11. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. *Leuk Res.* 2007;31:727-736.
12. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20:2429-2440.
13. Hackanson B, Robbel C, Wijermans P, et al. In vivo effects of decitabine in myelodysplasia and acute myeloid leukemia: review of cytogenetic and molecular studies. *Ann Hematol.* 2005;84(suppl 1):32-38.
14. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106:1794-1803.
15. Ruter B, Wijermans PW, Lubbert M. DNA methylation as a therapeutic target in hematologic disorders: recent results in older patients with myelodysplasia and acute myeloid leukemia. *Int J Hematol*. 2004;80:128-135.
16. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355:1456-1465.

Advances in the Treatment of Myelodysplastic Syndromes

A Review of Selected Presentations
From the 49th American Society of
Hematology Annual Meeting and Exposition
December 8–11, 2007
Atlanta, Georgia

817 Azacitidine Treatment Prolongs Overall Survival in Higher-Risk MDS Patients Compared With Conventional Care Regimens: Results of the AZA-001 Phase III Study[1]

P Fenaux, GJ Mufti, V Santini, C Finelli, A Giagounidis, R Schoch, AF List, SD Gore, JF Seymour, E Hellstrom-Lindberg, JM Bennett, JC Byrd, JT Backstrom, LS Zimmerman, DR McKenzie, CL Beach, LR Silverman

A previously reported randomized study comparing azacitidine versus best supportive care in MDS patients showed that azacitidine induced a significantly superior response rate (60% vs 7%, respectively: $P<.001$).[2] Additionally, an analysis of three separate trials found a trend toward improved overall survival (OS) in azacitidine-treated patients, although this was not statistically significant.[3] To expand on these findings, an international, multicenter, prospective phase III trial was conducted to determine the efficacy of azacitidine versus conventional care regimens; both treatment arms included a best supportive care component. A total of 358 higher-risk MDS patients were randomized to receive subcutaneous azacitidine 75 mg/m^2 daily on days 1–7 of each 28-day cycle (n=179) or a conventional care regimen consisting of either low-dose cytarabine, standard chemotherapy, or best supportive care only (n=179). In all cases, therapy was continued until either disease progression or an unacceptable adverse event.

At a median follow-up of 21.1 months, azacitidine produced a statistically significant improvement in median OS compared to the control group (24.4 vs 15 months; $P=.0001$; Figure 1). This corresponded to a hazard ratio (HR) of 0.58 (95% confidence interval [CI], 0.43–0.77) and an improvement in OS of 74%. Median OS per IPSS cytogenetic subgroup showed similar results (Table 1). At 2 years, OS for azacitidine-treated patients was approximately twice that of the control group (50.8% vs 26.2%; $P<.0001$). Azacitidine was well tolerated with safety data consistent with previous reports.

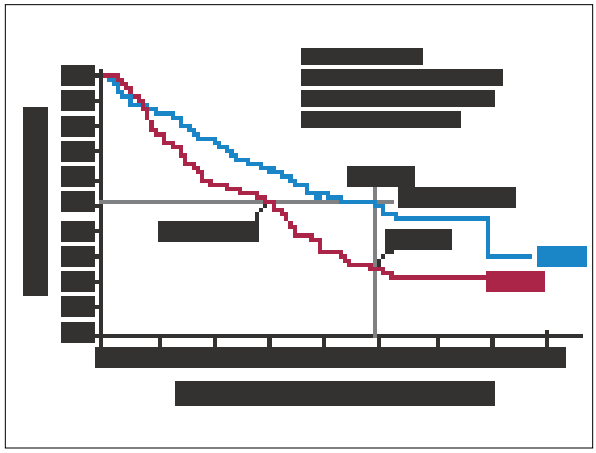

Figure 1. Overall survival: azacitidine (AZA) versus conventional care regimen (CCR) intent-to-treat (ITT) population.

CI=confidence interval; HR=hazard ratio.

This trial confirms and extends previous CALGB findings; further, it is the first MDS clinical study to demonstrate a significant OS advantage, thus altering the natural disease course. The authors concluded that azacitidine should be considered first-line therapy for higher-risk MDS patients.

Table 1. OS Analyses per IPSS Cytogenetic Group

Group	% (n/N) Pts	AZA Median, Months	CCR Median, Months	HR (95% CI)	Log-rank *P*
Good	46 (166/358)	Not reached	17.1	0.61 (0.39, 0.96)	.030
Intermediate	21 (76/358)	26.3	17.0	0.43 (0.21, 0.88)	.017
Poor	28 (100/358)	17.2	6.0	0.52 (0.32, 0.87)	.011

AZA=azacitidine; CCR=conventional care regimen; CI=confidence interval; HR=hazard ratio; IPSS=International Prognostic Scoring System; OS=overall survival.

818 Maintenance Treatment With Azacitidine for Patients With High Risk Myelodysplastic Syndromes or Acute Myeloid Leukemia in Complete Remission After Intensive Chemotherapy[4]

M Grövdal, R Khan, A Aggerholm, P Antunovic, J Astermark, P Bernell, LM Engström, L Kjeldsen, O Linder, L Nilsson, A Olsson, J Wallvik, JM Tangen, G Öberg, SE Jacobsen, P Hokland, A Porwit, E Hellström-Lindberg

Although several earlier studies have shown that induction therapy with intensive chemotherapy in patients with MDS or AML can achieve complete remission (CR) rates as high as 60%, these responses are generally short-lived and patients eventually relapse after 1 year.[5-8] Here, Grövdal and fellow authors sought to determine if maintenance therapy with azacitidine after achieving a CR with intensive chemotherapy can prolong response duration.[4]

Patients with either intermediate- or high-risk MDS or AML who could not receive curative treatment were eligible for inclusion in this study. The chemotherapy induction regimen was composed of 1 or 2 courses of daunorubicin (2–3 days) plus cytarabine (7 days). Patients achieving a CR then began maintenance therapy with low-dose azacitidine (5 days per 28-day cycle) for up to 2 years. The median patient age was 68 years (range: 54–83 years) and 67% were male. Most patients had a diagnosis of AML (62%), whereas the remaining patients had either MDS (28%) or CMML (10%). Cytogenetic prognoses, according to IPSS risk criteria, were as follows: 42% good; 17% intermediate; 28% poor; and 13% undetermined. Maintenance azacitidine after induction chemotherapy was well tolerated, although the original dose of 75 mg/m^2/day was reduced to 60 mg/m^2/day because of myelotoxicity.

Of the 60 total patients who enrolled, 24 (40%) achieved a CR. Although most baseline characteristics and pretreatment parameters did not significantly impact the likelihood of achieving a CR, higher levels of both white blood cells and CD34+ bone marrow cells decreased the likelihood of CR (*P*=.03 and *P*=.02, respectively). Additionally, increased CD34 expression was significantly associated with decreased OS (*P*=.036). At the time of the most recent follow-up the median duration of CR was 13.5 months; 7 patients (30%) maintained a CR at 20 months. Three of these 7 patients exhibited a trisomy 8 chromosomal aberration, a characteristic previously associated with superior response to azacitidine.[9]

A key finding of this study was the association of a poor response to induction chemotherapy with promoter DNA hypermethylation of one or more genes, assessed using denaturing gradient gel electrophoresis. Methylation of the promoters of three genes previously shown to impact response to treatment were analyzed: *P15INK4B* (*P15*), which encodes a cyclin-dependent kinase inhibitor; *CDH*, the gene for E-cadherin; and the hypermethylated in cancer-1 (*HIC1*) gene.[10] Although methylation of the *P15* promoter alone did not significantly decrease the rate of CR, promoter methylation of either *CDH* alone or *HIC1* alone did (*P*=.008 and *P*=.08, respectively; Figure 2). Additionally, patients with promoter methylation at both *P15* and either *CDH* or *HIC* had a greater decrease in CR (*P*=.05), and no patient with methylation evident at all three sites experienced a CR (*P*=.03). Interestingly, hypermethylation was significantly associated with high numbers of CD34+ bone marrow cells (*P*=.01), higher numbers of bone marrow blasts (*P*=.007), and AML compared with either MDS or CMML (*P*=.02). The methylation status of P15 did not significantly affect the duration of CR; however, methylation of *CDH* did significantly correlate with shorter OS (*P*=.005).

This study showed for the first time that promoter methylation could significantly negatively impact patient response to induction chemotherapy. Because of this finding, the study authors speculated that pretreatment with the hypomethylating agent azacitidine prior to induction therapy could improve patient response.

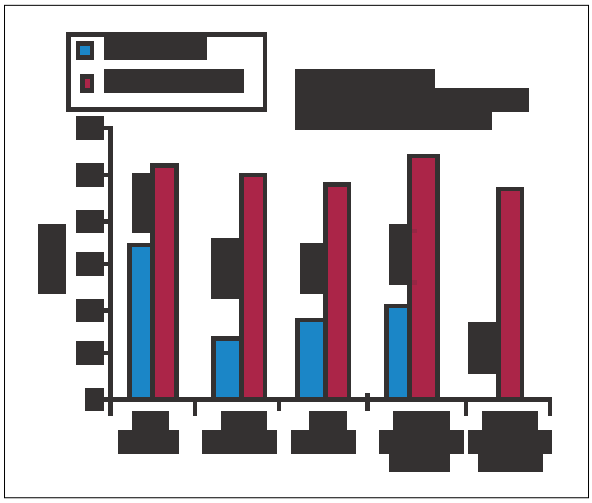

Figure 2. Promoter DNA hypermethylation of more than one analyzed gene is associated with a poor response to induction chemotherapy.

CR=complete response; MNC=bone marrow–derived mononuclear cell.

819 Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine in Patients With Myelodysplastic Syndromes[11]

RM Lyons, T Cosgriff, S Modi, H McIntyre, I Fernando, J Backstrom, CL Beach

Although azacitidine leads to disease improvement for patients with MDS, many patients find the frequent dosing schedule to be inconvenient.[12] To determine if alternative azacitidine regimens produce similar efficacy and safety, Lyons and colleagues initiated a phase II, prospective, multicenter, open-label study to evaluate three different dosing schedules.[11] Patients (N=151) were randomized to receive one of three regimens for six 28-day cycles; 139 were evaluable for assessment. A 2-day no-treatment period was included in two arms to test the possibility of eliminating weekend dosing. In the first regimen, AZA-5, patients received azacitidine 75 mg/m^2/day for 5 days (n=50); in the second regimen, AZA-5-2-2, patients received azacitidine 75 mg/m^2/day for 5 days, followed by 2 days of no treatment and then 2 additional days of 75 mg/m^2/day (n=50); the final regimen, AZA-5-2-5, consisted of azacitidine 50 mg/m^2/day for 5 days, followed by 2 days of no treatment and then 5 additional days at the 50 mg/m^2/day dose (n=51).

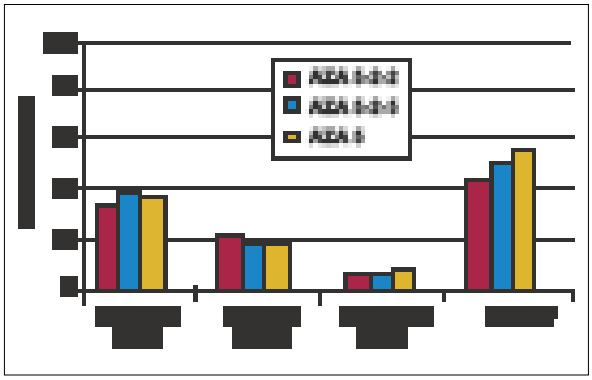

Figure 3. Hematologic improvement (HI) in response to three different azacitidine (AZA) treatment schedules.

*Patients counted only once for best response in an improvement category.
†Minor improvement at top of hematologic improvement columns.
.

A greater percentage of patients in the AZA-5 treatment group received 1 or more doses of therapy at each treatment cycle, compared to the other groups. Hematologic improvement was observed in 74 patients (53%) overall (AZA-5: n=28; AZA-5-2-2: n=22; AZA-5-2-5: n=24; Figure 3). Transfusion independence was achieved in 16, 12, and 12 patients in the AZA-5, AZA-5-2-2, and AZA-5-2-5 arms, respectively. In total, 55–63% of patients who were transfusion-dependent at baseline became transfusion-independent with treatment, generally by cycle 3. No new adverse effects were reported with these alternative dosing regimens, and the majority of grade 3 or 4 events were hematologic, including neutropenia, thrombocytopenia, anemia, leukopenia, and febrile neutropenia. The authors concluded that the alternative dosing regimens provide efficacy and tolerability consistent with the currently approved dose and clinicians may have flexibility in designing convenient alternative dosing regimens with no weekend dosing.

1458 Preliminary Results From a Phase I Study of [Lenalidomide] in Combination with [Azacitidine] in Patients With Advanced Myelodysplastic Syndromes[13]

MA Sekeres, A List, D Cuthbertson, R Paquette, T Loughran, JP Maciejewski

The primary goal of this phase I multicenter study was to determine the maximally tolerated dose (MTD) of the combination of lenalidomide with azacitidine, as well as

the associated dose-limiting toxicities induced by this treatment.[13] To determine the MTD, a classic 3 + 3 trial design was used, in which 3 individuals were entered on one dose level, which was escalated to the next dose level in the absence of any dose-limiting toxicity. Dose-limiting toxicities included grade 3 or 4 nonhematologic adverse effects or a greater than 50% drop in absolute neutrophil count or platelet count that was unrecovered by day 56. Azacitidine was subcutaneously administered at either 75 mg/m^2/day on days 1–5 (dose levels 1, 2, and 3) or 50 mg/m^2/day on days 1–5 and 8–12 (dose levels 4, 5, and 6). Lenalidomide was given orally at either 5 mg/day on days 1–14 (dose levels 1 and 4), 5 mg/day on days 1–21 (dose levels 2 and 5), or 10 mg/day on days 1–21 (dose levels 3 and 6). At the time of this report, a total of 12 patients had been enrolled in this ongoing trial.

Six evaluable patients had completed dose level 4 at the time of assessment, with no dose-limiting toxicities observed. As a result, a MTD had not yet been determined and further enrollment to increased doses is underway. Patients were also evaluated for response to this combination therapy. Though preliminary, the combination of azacitidine plus lenalidomide seems to be efficacious in these patients. Half of the evaluable patients (n=3) achieved a CR, and 2 achieved a neutrophil response. The final patient experienced progressive disease.

1459 Lenalidomide in High-Risk Myelodysplastic Syndrome and Acute Myelogenous Leukemia Associated With Chromosome 5 Abnormalities[14]

G Borthakur, G Garcia-Manero, S Faderl, Z Estrov, S Verstovsek, M Hood, H Kantarjian

Because of the dramatic activity of lenalidomide in MDS patients with a chromosome 5q deletion, Borthakur and colleagues designed this study to determine the efficacy and safety of lenalidomide in MDS and AML patients with any chromosome 5 abnormality.[14,15] Eligible patients had high-risk MDS or relapsed/refractory AML, an Eastern Cooperative Oncology Group (ECOG) performance score of less than or equal to 2, had not been previously exposed to lenalidomide, and had no known hypersensitivity to thalidomide. Patients with platelet counts at least 50,000/mL were administered 25 mg/day oral lenalidomide on days 1–21 of each cycle, and those with platelet counts below 50,000/mL received 15 mg/day oral lenalidomide on days 1–21 of each cycle. Cycles contained 28 days total. Dose interruptions and reductions were allowed as needed.

At the time of this report, 11 of a planned 30 patients had undergone treatment, 7 of whom were male. The median patient age was 63 years (range: 44–80), 6 patients had AML, and 5 had MDS. Eight patients had undergone a median of one prior therapy (range: 0–3). All 11 patients had at least one chromosomal abnormality, defined as either a complex karyotypic abnormality (n=9) or a single chromosomal abnormality in addition to a 5q deletion (n=2).

A positive response to lenalidomide was observed in 2 patients. The first patient, who achieved a CR after receiving three cycles of therapy, had a karyotypic abnormality of trisomy 8 in addition to a 5q deletion. The second patient experienced a reduction in bone marrow blasts from 21% to 5%. However, this patient suffered from severe thrombocytopenia complicated by gastrointestinal bleeding and had to discontinue lenalidomide treatment, eventually undergoing disease progression. Of the remaining patients, 8 experienced disease progression and 1 underwent stem cell transplantation. Grade 3 or 4 adverse events resulted in the need for dose interruptions in 6 patients (55%), and 3 patients required dose reductions.

The authors concluded that the role of lenalidomide in the treatment of high-risk MDS and AML with chromosome 5 and additional karyotypic abnormalities needs to be defined in the context of clinical trials and future studies are needed to examine lower doses with or without growth factor support.

820 Lenalidomide in INT 2 and High Risk MDS With Del 5q: Interim Results of a Phase II Trial by the GFM[16]

S Burcheri, T Prebet, O Beyne-Rauzy, RM Mbida, N Hoarau, L Legros, C Ravoet, F Dreyfus, A Stamatoullas, MP Chaury, J Delaunay, G Laurent, N Vey, L Ades, C Gardin, P Fenaux

Although lenalidomide is a standard treatment for low- and intermediate-1–risk MDS patients with a chromosome 5q deletion, its activity in higher-risk patients is largely unknown.[15,17] Burcheri and colleagues initiated this phase I/II multicenter study to determine the activity of lenalidomide in higher-risk patients.[16] Patients enrolled in this trial were required to have both MDS with a deletion at chromosome 5q and a high- or intermediate-2–risk IPSS score. Single-agent lenalidomide was initially administered at a dose of 10 mg daily for 21 consecutive days of a 28-day cycle. In the absence of a response after 8 weeks, lenalidomide was increased to 15 mg daily. A

total of 49 patients were included, 41 of whom were evaluable and included in this data analysis. A total of 8 patients had a sole chromosomal abnormality of a 5q deletion, whereas 9 had a 5q deletion plus an additional abnormality, and 24 had a 5q deletion and more than one additional abnormality (considered complex).

Of the 37 evaluable patients who completed one cycle, 4 achieved a CR, an additional 2 achieved a marrow CR, and 2 experienced hematologic improvement. The overall response rate was therefore 21%. Cytogenetic responses were observed in 6 patients, 3 of which were complete. Importantly, patients who had either a 5q deletion only or a baseline platelet count of greater than 100×10^9 cells/L experienced higher rates of CR (37% and 31%, respectively) than patients with complex karyotypes (8%) or platelet counts less than 100×10^9 cells/L (<1%). After a median follow-up of 300 days, 3 of 4 patients achieving a CR and 1 of 2 patients with a marrow CR maintained their responses.

After a median follow-up of 300 days, a total of 13 patients had died. In addition, all 37 evaluable patients experienced grade 4 thrombocytopenia and several patients exhibited grade 4 neutropenia despite the use of granulocyte colony-stimulating factor (G-CSF). These hematologic toxicities resulted in dose reductions in 40% of patients and the exclusion of 13 patients after completion of cycle 1. Additionally, 80% of patients required hospitalization during cycle 1. This led the authors to conclude that, although lenalidomide may be effective in these patients, further studies are required to determine the best dose.

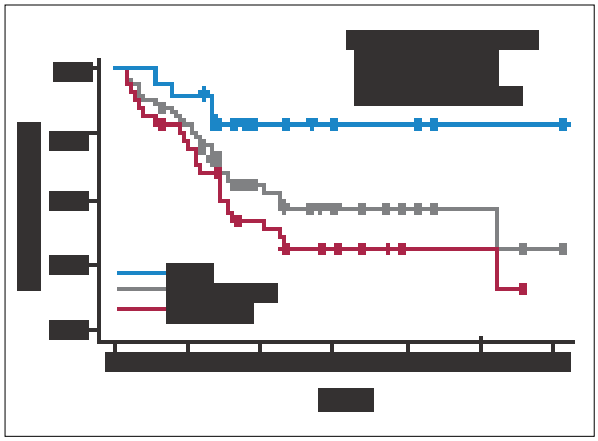

Figure 4. Azacitidine + MGCD0103: overall survival.

Hazard ratio of 0.337 (66% reduction in risk of death) for responder versus nonresponder; *P*=.006.

444 Phase I/II Study of MGCD0103, an Oral Isotype-Selective Histone Deacetylase Inhibitor, in Combination with 5-Azacitidine in Higher-Risk Myelodysplastic Syndrome and Acute Myelogenous Leukemia[18]

G Garcia-Manero, AS Yang, V Klimek, J Cortes, F Ravandi, WM Newsome, J Dumouchel, M Dubay, Z Li, C Maroun, E Laille, H Kantarjian, RE Martell, S Luger

MGCD0103 is a new histone deacetylase (HDAC) agent with selectivity for the 1 and 2 HDAC isoforms.[19] In vitro treatment of leukemia cells has shown single-agent MGCD0103 can induce cell death, and phase I trials have shown it to have activity in leukemia patients with a relatively good safety profile.[20] Interestingly, the combination of MGCD0103 with azacitidine produces a synergistic cell death response in vitro. In this report, Garcia-Manero and fellow investigators tested this combination in patients with MDS and AML.[18] A total of 52 patients with an ECOG performance status of 2 or less were enrolled in this study, including both treatment-naive (n=15) and relapsed or refractory (n=37) individuals.

To determine the MTD of MGCD0103 when combined with azacitidine, a classic 3 + 3 study design was employed in the phase I portion of the trial. Azacitidine was administered at a fixed dose (75 mg/m^2 subcutaneously) daily for the first 7 days of a 28-day cycle. Starting on day 5, oral MGCD0103 was given three times per week at escalating doses: 35 mg (n=3), 60 mg (n=3), 90 mg (n=6), 110 mg (n=3), and 135 mg (n=4). The MTD for MGCD0103 was initially determined to be 110 mg, but excess toxicity at this dose as the patient group expanded caused the dose to be lowered to 90 mg, the dose used in the phase II portion of the trial. Of the patients who received the 90 mg dose of MGCD0103 in both the phase I and II portions of the study (n=19), 4 experienced a grade 3 toxicity and none had a grade 4 toxicity. In the 52 patients included in the study, drug-related nonhematologic grade 3 and 4 toxicities included fatigue, nausea, vomiting, anorexia, dehydration, diarrhea, and asthenia. These toxicities were reported in patients who received at least one treatment cycle.

Coadministration of MGCD0103 resulted in HDAC inhibition in 12 of 13 patients tested; the patient with no inhibition received the lowest dose of 35 mg. Of the 52 total patients, the overall response rate was 36% with 8 CRs, 10 CRs with incomplete blood recovery (CR-i), and 1 partial response. A median of 2 cycles (range: 1–4) were given before a response was achieved. Importantly, at the MTD of 90 mg used to treat 19 patients in the

phase I and II portions combined, the overall response rate was 53%: 4 CR and 6 CR-i. The median number of cycles administered prior to a response in this subgroup of patients was 1.5 (range: 1–4). Additionally, the overall response rate was higher among treatment-naive (n=15) versus relapsed or refractory (n=37) patients (53% vs 30%, respectively).

The median OS was significantly improved in responding patients versus nonresponding patients (not reached vs 148 days, respectively; *P*=.006; Figure 4). A total of 4 of 19 responding patients died, compared with 22 of 33 nonresponding patients (HR=0.337). This corresponded to a 66% reduction in the risk of death for responding versus nonresponding patients. The promising activity of this combination along with its manageable toxicity profile has led to the design of a larger randomized study to further investigate its efficacy.

115 Survival and Efficacy of Decitabine in Myelodysplastic Syndromes, Analysis of the 5-Day IV Dosing Regimen[21]

H Kantarjian, G Garcia-Manero, S O'Brien, Z Estrov, F Ravandi, J Cortes, J Shan, J Davisson, JP Issa

A second hypomethylating agent, decitabine, has also received approval for the treatment of MDS.[22,23] The purpose of this current study, presented by Kantarjian and fellow investigators, was to evaluate the long-term efficacy of decitabine in MDS.[21] To evaluate this, the authors provided updated results of a previously reported randomized trial of three different decitabine dosing schedules.[24] In the initial report, a low dose of decitabine administered intravenously over 5 days was found to have significant activity in MDS patients. Therefore, that dosing schedule was used to determine the long-term efficacy of decitabine.

A total of 124 MDS patients were included in this trial, 27% of whom had secondary MDS. Patients were randomized to one of three decitabine dosing arms, all of which administered 100 mg/m^2 over each course, but were differently distributed: 20 mg/m^2/day administered intravenously over 5 days (5D-IV), 20 mg/m^2/day administered subcutaneously over 5 days (5D-SQ), or 10 mg/m^2/day administered intravenously over 10 days (10D-IV). These courses were repeated every 4–6 weeks.

Overall response rates were similar among the three arms (72%, 70%, and 78% for 5D-IV, 5D-SQ, and 10D-IV, respectively). Importantly, a number of these were CRs (39%, 21%, and 24%, respectively). The median OS for all 124 patients was 20 months, but was

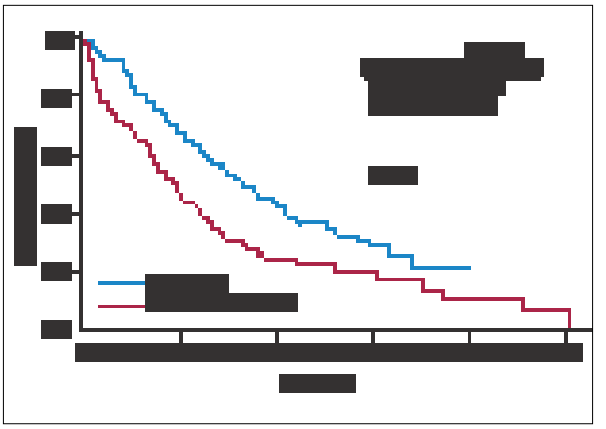

Figure 5. Decitabine survival versus intensive chemotherapy in higher risk myelodysplastic syndromes (matched group).

Adapted from Kantarjian H, et al. *Blood*, 2007; 110: 42a-43a. Abstract 115.

significantly improved in treatment-naive patients compared with those who had received prior therapy (30 vs 15 months; *P*=.008). Additionally, patients with an IPSS risk of intermediate-2 or high had significantly decreased OS compared with intermediate-1–risk patients (25 months vs not reached, respectively; *P*=.07).

Also presented was an analysis comparing decitabine treatment with intensive therapy. Results for the 124 patients in the decitabine trial were compared with those of 115 baseline-matched historical controls who had received intensive therapy in the 10 years prior to the decitabine study. Responses were similar for the two cohorts, with CRs seen in 44% of decitabine-treated patients and 46% of controls and partial responses noted in 2% and 0% of patients, respectively; however, a larger number of deaths occurred in patients receiving the intensive therapy compared to decitabine, both at 6 weeks (13 vs 3 deaths, respectively) and 3 months (23 vs 8 deaths, respectively). Importantly, the median OS was also significantly improved in decitabine-treated patients compared with intensive chemotherapy–treated patients (20 vs 12 months, respectively; *P*=.001; Figure 5).

1450 Preliminary Results of a Phase II Study of Decitabine Administered Daily for 5 Days Every 4 Weeks to Adults with Myelodysplastic Syndrome[25]

DP Steensma, MR Baer, JL Slack, R Buckstein, L Godley, JS Larsen, MT Cullen, HM Kantarjian

The previously reported pilot study of alternative doses of decitabine found a 5-day regimen to be both safe and

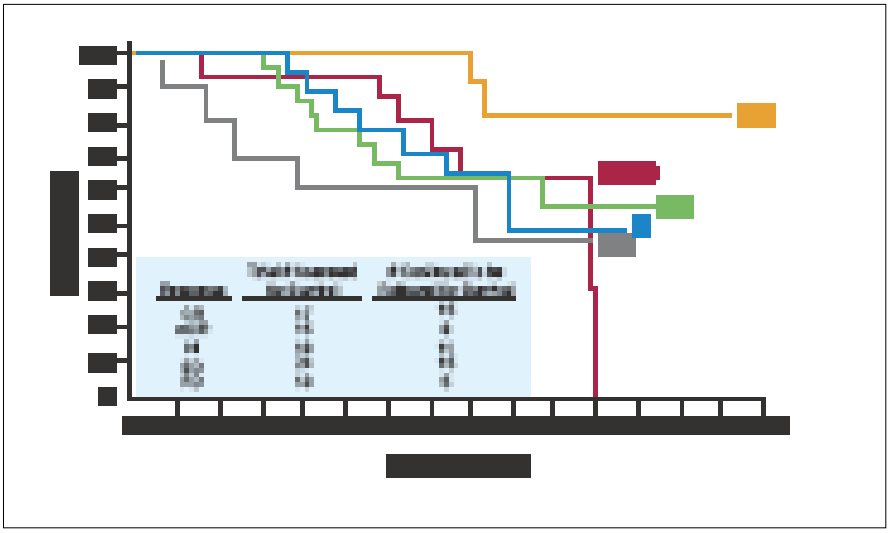

Figure 6. Overall survival by response. Complete responses were associated with better overall survival.

*Not evaluable patients were not included in this analysis.

†Drop is due to 2 patient deaths at data cut-off (May 31, 2007). Eight patients in this group (mCR) are alive and continue to be followed for survival.

efficacious in MDS patients.[24] To confirm these findings, a phase II multicenter study was initiated. Here, Steensma and colleagues report the preliminary results of this open-label nonrandomized study, which included patients with advanced MDS.[25] Patients had diverse diagnoses of MDS, an ECOG performance status of not more than 2, and had not received any chemotherapy for a minimum of 4 weeks prior to initiating decitabine. The distribution of IPSS risk groups was as follows: 1% low, 53% intermediate-1, 23% intermediate-2, and 23% high. Nearly half (49%) of patients had a good cytogenetic risk, while 15% had an intermediate risk and 29% had a poor risk; the cytogenetic risk was unknown in 6% of patients.

Decitabine (20 mg/m^2) was given intravenously for 5 consecutive days, a cycle which was repeated every 4 weeks. At the time of this evaluation, patients had received a median of 5 cycles (range: 1–17 cycles) and 38% of patients had received at least 8 treatment cycles. Of the 99 patients treated, 84 were eligible for evaluation. In these patients, the overall response rate was 38%, all of which were either a CR or marrow CR. Additionally, 21% of patients exhibited hematologic improvement. Progressive disease was observed in 12% of patients. Response to decitabine was rapid and clinical improvement occurred by cycle 2 in 82% of patients (median time to improvement: 1.7 months). Moreover, the decitabine-induced improvement was durable, lasting a median of 10 months at time of cut-off. Patients receiving decitabine experienced a 1-year OS rate of 66%, with a median OS of 19.4 months. Importantly, patients achieving a CR to decitabine experienced improved rates of OS compared with those not responding as effectively (Figure 6).

Grade 3 or higher hematologic toxicities were as follows: neutropenia 37%, thrombocytopenia 22%, anemia 21%, febrile neutropenia 17%, and pancytopenia 5%. Other, nonhematologic, adverse events were also reported. The authors concluded that decitabine administered daily for 5 days in the outpatient setting demonstrates clinical activity with a manageable toxicity profile in intermediate-1– to high-risk MDS, suggesting that both the 3- and 5-day regimens provide meaningful clinical benefit to patients.

250 Phase 1/2 Study of AMG 531 in Thrombocytopenic Patients with Low-Risk Myelodysplastic Syndrome: Update Including Extended Treatment[26]

H Kantarjian, P Fenaux, MA Sekeres, P Becker, A Boruchov, D Bowen, R Larson, R Lyons, P Muus, J Shammo, M Ehrman, K Hu, Janet Nichol

AMG 531 is a thrombopoiesis-stimulating Fc-peptide fusion protein (peptibody) currently under investigation for its ability activate the thrombopoietin receptor and improve platelet production.[27] Here, Kantarjian and colleagues reported on the extension phase of the first portion of an ongoing phase I/II open-label sequential-cohort study to determine the safety and efficacy of AMG 531 in patients with low-risk MDS and severe thrombocytopenia.[26] In this study low-risk MDS was defined as IPSS low- or intermediate-1–risk (excluding CMML) and severe thrombocytopenia was considered less than or equal to 50 cells/mL. Only patients receiving best supportive care alone were eligible for this study.

Sequential cohorts of patients were included in a dose escalation of 300, 700, 1,000, and 1,500 mg AMG 531 administered in three weekly subcutaneous injections. After 4 weeks, patient platelet response was evaluated, at which time patients could opt to continue AMG 531 therapy in the extension phase of the trial. During this extension phase, patients could either continue at their assigned dose of AMG 531 or adjust their dose to achieve or maintain a response.

Patients received AMG 531 therapy for a mean duration of 23±15.5 weeks. Of the original 44 patients enrolled in the dose escalation portion of the study, 40 opted to continue into the extension phase. At the time of this report, 16 patients continued therapy. A platelet response was achieved in 18 patients (41%). This response was considered durable, with a mean duration of 22.8±13.3 weeks. A total of 104 platelet transfusions were required during the study, but only 7 of these were given to patients who had achieved a durable platelet response.

Treatment-related adverse events occurred in 17 patients, along with 2 cases of transformation to AML. Temporary blast cell increases were confirmed in 6 patients, 2 of whom were receiving 1,000 µg AMG 531 and 4 of whom were receiving 1,500 µg; blasts decreased within 7 weeks after discontinuation of therapy. Additionally, 3 deaths occurred, none of which was considered related to the study.

References

1. Fenaux P, Mufti GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 phase III study. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 817.
2. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429-2440.
3. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol*. 2006;24(24):3895-3903.
4. Grövdal M, Khan R, Aggerholm A, et al. Maintenance treatment with azacitidine for patients with high risk myelodysplastic syndromes or acute myeloid leukemia in complete remission after intensive chemotherapy. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 818.
5. Knipp S, Hildebrand B, Kundgen A, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. *Cancer*. 2007;110:345-352.
6. Kantarjian H, Beran M, Cortes J, et al. Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. *Cancer.* 2006;106(5):1099-1109.
7. Hast R, Hellstrom-Lindberg E, Ohm L, et al. No benefit from adding GM-CSF to induction chemotherapy in transforming myelodysplastic syndromes: better outcome in patients with less proliferative disease. *Leukemia*. 2003;17(9):1827-1833.
8. Hofmann WK, Heil G, Zander C, et al. Intensive chemotherapy with idarubicin, cytarabine, etoposide, and G-CSF priming in patients with advanced myelodysplastic syndrome and high-risk acute myeloid leukemia. *Ann Hematol.* 2004;83(8):498-503.
9. Najfeld V, Scalise A, Odchimer-Reissig R, et al. The modulating effect of azacitidine (Aza C) on the cytogenetically tracked MDS clone impact survival. Presentation at the 46th Annual American Society of Hematology Annual Meeting and Exposition; San Diego, CA; December 4-7, 2004. Abstract 1429.
10. Grovdal M, Khan R, Aggerholm A, et al. Negative effect of DNA hypermethylation on the outcome of intensive chemotherapy in older patients with high-risk myelodysplastic syndromes and acute myeloid leukemia following myelodysplastic syndrome. *Clin Cancer Res*. 2007;13(23):7107-7112.
11. Lyons RM, Cosgriff T, Modi S, et al. Results of the initial treatment phase of a study of three alternative dosing schedules of azacitidine (Vidaza®) in patients with myelodysplastic syndromes (MDS). Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 819.
12. Pharmion. Vidaza full prescribing information. www.vidaza.com.
13. Sekeres MA, List A, Cuthbertson D, et al. Preliminary results from a phase I study of Revlimid® (lenalidomide) in combination with Vidaza® (azacitidine) in patients with advanced myelodysplastic syndromes (MDS). Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007:Abstract 1458.
14. Borthakur G, Garcia-Manero G, Faderl S, et al. Lenalidomide in high-risk myelodysplastic syndrome and acute myelogenous leukemia associated with chromosome 5 abnormalities. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 1459.
15. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355:1456-1465.
16. Burcheri S, Prebet T, Beyne-Rauzy O, et al. Lenalidomide (LEN) in INT 2 and high risk MDS with DEL 5q. Interim results of a phase II trial by the GFM. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 820.
17. Giagounidis AA, Haase S, Heinsch M, et al. Lenalidomide in the context of complex karyotype or interrupted treatment: case reviews of del(5q)MDS patients with unexpected responses. *Ann Hematol*. 2007;86(2):133-137.
18. Garcia-Manero G, Yang AS, Klimek V, et al. Phase I/II study of MGCD0103, an oral isotype-selective histone deacetylase (HDAC) inhibitor, in combination with 5-azacitidine in higher-risk myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 444.
19. Khan N, Jeffers M, Kumar S, et al. Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. *Biochem J*. 2008;409(2):581-589.
20. Lancet JE, Nichols G, Assouline S, et al. A phase I study of MGCD0103 given as a twice weekly oral dose in patients with advanced leukemias or myelodysplastic syndromes (MDS). *J Clin Oncol*. 2007;25(18S):Abstract 2516.
21. Kantarjian H, Garcia-Manero G, O'Brien S, et al. Survival and efficacy of decitabine in myelodysplastic syndromes (MDS), analysis of the 5-day IV dosing regimen. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 115.
22. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8):1794-1803.
23. Kantarjian HM, O'Brien S, Huang X, et al. Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome: comparison with historical experience. *Cancer*. 2007;109:1133-1137.
24. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007;109(1):52-57.
25. Steensma DP, Baer MR, Slack JL, et al. Preliminary results of a phase II study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndrome (MDS). Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 1450.
26. Kantarjian H, Fenaux P, Sekeres MA, et al. Phase 1/2 study of AMG 531 in thrombocytopenic patients (pts) with low-risk myelodysplastic syndrome (MDS): update including extended treatment. Presentation at the 49th Annual American Society of Hematology Annual Meeting and Exposition; Atlanta, Georgia; December 8-11, 2007. Abstract 250.
27. Evangelista ML, Amadori S, Stasi R. Biologic aspects of thrombopoietin and the development of novel thrombopoietic agents for clinical use. *Curr Drug Discov Technol.* 2007;4(3):162-173.

Commentary

Guillermo Garcia-Manero, MD

Chief, Section of MDS, Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston, Tex.

It was a remarkable year for investigators of azacitidine. Fenaux and colleagues (abstract 817) presented the results of a randomized phase III study of azacitidine versus conventional care, with 179 patients on each arm. The primary endpoint was OS. The OS for azacitidine was 24.4 months versus 15 months for conventional care (*P*=.0001). The 2-year OS was 51% for patients on azacitidine and 26% for conventional care regimens (*P*=.0001). The overall response rate was also significantly higher with azacitidine than for conventional care. These are very important results, as they confirm for the first time a significant benefit in terms of OS, thereby establishing azacitidine as first-line therapy in patients with higher-risk MDS. These results also have significant implications for clinical trial design and the role of other therapies (decitabine, lenalidomide) in this patient population.

A key aspect of the above presentation was the fact that the median number of cycles administered was nine, indicating the need for continuous treatment administration for maximal clinical benefit. Following this argument, Grövdal and colleagues presented results (abstract 818) from a study of consolidation/maintenance therapy with azacitidine in patients that had received standard induction therapy with daunorubicin plus cytarabine. Patients were older with high-risk MDS or AML. Azacitidine was intended to be administered indefinitely. Median survival in this single-arm poor-risk group was 17 months, a significant duration compared to standard approaches, which are not well defined in this patient population.

An important issue with azacitidine is dose schedule, as the FDA-approved 7-day schedule is difficult to use in many community centers. Lyons et al (abstract 819) compared three common schedules of azacitidine: 5-day, 5-2-2 (weekend off), and 5-2-5 reduced-dose. Results indicated no differences in terms of activity between the three schedules and a better myelosuppression profile with the 5-day schedule. That said, the impact of the 5-day schedule on survival is unknown and it is difficult to extrapolate the 7-day schedule survival data to the 5-day schedule. Therefore, physicians that can administer this drug for 7 days should continue to do so, and those who cannot can probably switch to a 5-day schedule.

It is now well established that the combination of azacitidine with HDAC inhibitors is safe and active in MDS/AML. MGCD0103 is an oral HDAC inhibitor with activity in AML. My group (abstract 444) presented the results of a phase I/II study of this combination. The overall response rate (CR, CR-i) in patients with previously untreated disease was above 50% with a median of 1–2 courses to response. Although these results are promising, the role of the combination needs to be assessed in a randomized study, which is planned to start early 2008. Another interesting study was presented by Sekeres and associates (abstract 1458) with the combination of azacitidine and lenalidomide. Although preliminary, it appears that the combination may be safe and active.

Two important studies with decitabine were presented. Kantarjian et al updated the results of the 5-day schedule of decitabine (abstract 115) from an original randomized phase II study of different schedules. In this study of poor-risk patients with MDS the CR was 39% and clinical benefit was observed in close to 80% of patients. The median number of courses was 10. A confirmatory phase II trial of decitabine using the 5-day schedule was presented by Steensma and colleagues (abstract 1450). The overall response rate was 38%, with all of these responses stemming from CRs or marrow CRs. The differences between these two studies in terms of outcome are not clear, in particular the number of courses of therapy administered (10 vs 5) and response rates.

Two studies (abstracts 1459 and 820) explored the use of lenalidomide in higher-risk MDS with deletion of chromosome 5. The studies showed limited clinical activity, which was mainly observed in patients without thrombocytopenia. Lenalidomide was associated with significant myelosuppression and an almost 100% risk of admission to hospital. These data indicate that although the clinical activity of single-agent lenalidomide is limited in this group of patients it may have a role in combination approaches or using other dose schedules (eg, short higher-dose intervals).

Finally, the data on AMG 531 (abstract 250) indicated a response rate, in terms of platelet improvement, of 40% in patients with lower-risk MDS and thrombocytopenia, although transient increases in blasts and leukocytosis were observed in a subset of these patients. Combination studies of AMG 531 with lenalidomide and hypomethylating agents are ongoing and should be of interest.

The therapeutic options for patients with MDS are now formidable. The azacitidine survival data are extremely important: for the first time, we have evidence that any therapeutic intervention is associated with improved survival in MDS. Further studies with decitabine and lenalidomide will help establish the role of these three agents in this disease for specific groups of patients.

Advances in the Treatment of Myelodysplastic Syndromes

CME Post-Test: *Circle only one answer per question.*

1. In a study reported by Fenaux and colleagues, azacitidine treatment significantly improved median OS compared to the control group, from _____ to _____ months.

   a. 17.2; 26.3
   b. 15; 24.4
   c. 17.2; 24.4
   d. 15; 39.2

2. Methylation of the CDH gene promoter was associated with a decreased rate of CR in response to _____ treatment, in a study presented by Grövdal and investigators.

   a. azacitidine
   b. decitabine
   c. lenalidomide
   d. MGCD0103

3. Hematologic improvement occurred in _____ of all patients receiving one of three dose regimens of azacitidine, in a trial performed by Lyons and colleagues.

   a. 28%
   b. 32%
   c. 48%
   d. 53%

4. True or false: An MTD of 5 mg daily over 14 days of lenalidomide in combination with azacitidine was determined in a report by Sekeres and fellow authors.

   a. True
   b. False

5. Of 11 patients included in an assessment by Borthakur and colleagues, a positive response to _____ was observed in 2 individuals.

   a. lenalidomide
   b. azacitidine
   c. decitabine
   d. MGCD0103

6. Interim results of a phase II study by Burcheri and associates found an OR rate of _____ among patients with high-risk MDS treated with lenalidomide.

   a. 16%
   b. 20%
   c. 21%
   d. 37%

7. When combined with azacitidine, the MTD of MGCD0103 was determined to be _____ after excess toxicity caused the initial MTD to be lowered.

   a. 35 mg
   b. 60 mg
   c. 75 mg
   d. 90 mg

8. When compared to intensive chemotherapy, decitabine significantly improved the median OS of MDS patients to _____ in a study by Kantarjian and colleagues.

   a. 12 months
   b. 16 months
   c. 18 months
   d. 20 months

9. In a trial evaluating alternative doses of decitabine, by Steensma and colleagues, patients receiving decitabine had a 1-year OS rate of _____.

   a. 19.4%
   b. 38%
   c. 66%
   d. 82%

10. True or false: AMG 531 is a novel peptibody that stimulates platelet production through activation of the thrombopoietin receptor.

    a. True
    b. False

Evaluation Form—Advances in the Treatment of Myelodysplastic Syndromes

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
(1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree)

1. Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- Discuss findings from studies presented at ASH 2007 on the treatment of MDS. 1 2 3 4 5
- Review the results of these new study findings, including clinical trials evaluating new treatment options in MDS. 1 2 3 4 5
- Select the latest knowledge and methods for treating patients with MDS with newly available options related to the applicability to clinical practice. 1 2 3 4 5
- Identify future research directions for the treatment of MDS. 1 2 3 4 5

2. Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

3. Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity: _____

Please list any topics you would like to see addressed in future educational activities: _____

_____

Additional comments about this activity: _____

_____

4. Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests/Evaluation by Course" and search by project ID 5119. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Posttest Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, ZIP _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

For Physicians Only

I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1.0 credit. ☐ I participated in only part of the activity and claim _____ credits.