

Recent Trends in the Treatment of MDS

Highlights from the 11th Congress of the
European Hematology Association

June 15–18, 2006
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Introduction

The myelodysplastic syndromes (MDS) are a relatively heterogeneous group of disorders that are characterized by one or more peripheral blood cytopenias secondary to bone marrow dysfunction. The major clinical problems are therefore morbidities that are caused by these cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). MDS can arise either *de novo* or as secondary MDS after treatment with chemotherapy and/or radiotherapy for other diseases, or due to an increasing number of other chemical-related and lifestyle-related causative factors. Indeed, a number of recent reports indicate that close hematologic monitoring should be carried out during chemotherapy in the treatment of various diseases.²⁻⁷

Estimates of the incidence of MDS are varied, with 5/100,000 of the general population suggested⁸; with MDS occurring mainly in older patients, the rate rises to 22–45/100,000 among those over age 70. However, an incidence of 1/500 people over the age of 60 years has also been suggested,⁹ and, indeed, MDS appears to be the most common hematologic malignancy in this age group. Therefore, the management of MDS is complicated by the generally advanced age of patients (although MDS in a 2-year-old patient has been reported¹) and nonhematologic comorbidities.

The common early signs of MDS include anemia, bleeding, easy bruising, and fatigue, and it is sometimes accompanied by splenomegaly or hepatosplenomegaly. Around 50% of patients with MDS also show detectable cytogenetic abnormalities, mainly deletions of all or part of chromosome 5 (del 5/5q) or 7 (del 7/7q) or trisomy 8. Once diagnosed, it immediately becomes important for patients with MDS to be defined according to their clinical status for their diagnostic and prognostic classification, and hence for their potential treatment options.

The mainstay of treatment for MDS remains supportive care,⁸ with anemia being treated with regular red cell transfusions. Patients undergoing chronic red cell transfusions may require iron chelation. Of note, following the initial diagnosis of MDS, there are essentially two therapeutic aims: (i) for lower-risk patients, the major

therapeutic aim is for hematologic improvement; (ii) for higher-risk patients, the main aim is alteration of the natural progression of MDS.

However, there are now new and emerging therapeutic options available (Table 1), although few of these have been approved for general use in patients with MDS and several are currently available only to patients enrolled in clinical trials.^{8,10,11} Indeed, given the rapid advances that are taking place in the treatment of patients with MDS, it has become essential for physicians to keep themselves apprised of the most recent therapies as they are reported.

At the 11th Congress of the European Hematology Association, which took place June 15–18, 2006, in Amsterdam, Netherlands, several presentations addressed recent treatment trends in MDS. Therapeutic advances such as the development of lenalidomide (Revlimid, Celgene) and other agents were highlighted, as were various aspects of the MDS patient management. The following offers a summary of these various presentations, emphasizing overall the significant advances that have been made in the care of patients with MDS.

The Evolution of the MDS Classification, Prognosis, and Response Systems

Over the past 20 years or so, there have been many prognostic scoring systems considered for patients with MDS.¹²⁻¹⁴ The introduction of the French-American-British (FAB) classification for predicting prognosis and evolution to AML based upon morphology, survival, and blast number significantly advanced the clinical utility of the scoring system.¹⁵ Also used widely is the International Prognostic Scoring System (IPSS),¹⁶ a risk-based system, which includes time to AML, percentage blasts, karyotype, and percentage cytopenias. In addition, the World Health Organization (WHO) classification of the myeloid neoplasms incorporates many of the concepts and definitions of the FAB system, with refined definitions of some of the FAB subtypes formulated to improve their clinical relevance.¹⁷⁻¹⁸

Although these main systems for classification and prognosis for MDS have been regularly compared, con-

Table 1. Drug Treatment Options for Patients With MDS^{8,10,11}

Agent	Proprietary Name (Company)	Mode of Action	Route of Administration	US FDA Approval/ Indication
Amifostine	Ethylol (MedImmune)	Chemoprotective agent	SC	Cancer
Antithymocyte globulin	Atgam (Pfizer); Thymoglobulin (IMTIX Sangstat)	Immunosuppressive agent; polyclonal antibody	IV	Moderate to severe aplastic anemia
Arsenic trioxide	Trisenox (Cephalon)	Activation of apoptosis; inhibition of angiogenesis; suppression of cellular proliferation	IV	Acute promyelocytic leukaemia
Azacitidine	Vidaza (Pharmion)	DNA hypomethylation	SC	MDS
Cyclosporin	Neoral, Sandimmune (Novartis)	Immunosuppressant	PO	Prevention of rejection of kidney, liver, and heart transplants
Darbepoietin alfa	Aranesp (Amgen)	Growth factor	SC	Anemia with kidney failure or with cancer and cancer treatments
Decitabine	Dacogen (MGI Pharma/SuperGen)	DNA hypomethylation	IV	MDS
Deferasirox ICL 670	Exjade (Novartis)	Iron chelator	PO	Removal of excess iron from the body
Deferoxamine	Desferal (Novartis)	Iron chelator	SC/IV	Removal of excess iron from the body
Epoetin alfa Erythropoietin	Epogen (Amgen); Procrit (Ortho Biotech)	Erythropoietic growth factor	SC	Anemia associated with kidney failure, cancer therapies, AIDS, or surgery
G-CSF Filgrastim	Neupogen (Amgen)	Hematopoietic growth factor	IV/SC	Cancer treatments
GM-CSF Sargramostim	Leukine (Berlex)	Hematopoietic growth factor	IV/SC	Cancer treatments
Lenalidomide	Revlimid (Celgene)	Immunomodulatory, antiangiogenic, antineoplastic	PO	Transfusion-dependent del(5q) MDS, multiple myeloma
Mycophenolate mofetil	Cellcept (Roche)	Immunosuppressive	PO	Phase II studies in MDS and aplastic anemia ongoing
R115777 Tipifarnib	Zarnestra (Johnson & Johnson)	Farnesyl transferase inhibitor	PO	Phase II studies in MDS ongoing
Thalidomide	Thalomid (Celgene)	Immunomodulatory, antiangiogenic, anti-inflammatory	PO	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum, multiple myeloma
TLK-199	Telintra (Telik)	Stimulation of bone marrow	PO/IV	Phase II studies in MDS ongoing
Topotecan	Hycamtin (GlaxoSmithKline)	Topoisomerase I inhibitor	IV	-
VNP40101M	Cloretazine (Vion)	Sulfonylhydrazine alkylating agent; cross-linking of DNA	PO	Phase II studies in MDS ongoing

IV = intravenous; MDS = myelodysplastic syndromes; PO = oral; SC = subcutaneous; TNF = tumor necrosis factor.

Table 2. Preferred Therapeutic Approach for Treating MDS According to Risk Category*

Agent	Median Ranking by Respondents [†]			
	Low Risk	Int-1 Risk	Int-2 Risk	High Risk
Azacitidine	2.5	3	2	2
Amifostine	8	8	8	8
Arsenic trioxide	7	7	6	6.5
Calcitriol	7.5	7.5	8	8
Lenalidomide	2	2.5	3	7
Decitabine	3	2	2.5	3
Oral chelation therapy	2	2	4	4.5
Thalidomide	5	5.5	6	7

* Clinicians were asked: Based on the information available to you, which of the drugs currently under investigation do you feel will be the most useful in treating MDS?¹⁹

[†] Scale 1–8; 1 = most useful; 8 = least useful.

trasted, and updated, it is of particular interest here to compare their use not just under the well-defined conditions of clinical trials, but also in the real-world situation of the expert practitioner. This was an aspect reported by Ghulam J. Mufti, MD, of the School of Medicine at Kings College Hospital, London, in a survey of the practices and treatment of patients with MDS.¹⁹ These data were obtained from the 106 academic medical centers with clinical research and/or diagnostic programs in MDS that have been designated Centers of Excellence within the framework of the MDS Foundation, Inc., an international nonprofit organization established by physicians and researchers to foster the exchange of information. Although the full dataset obtained from the 71 centers (US, 41; Europe, 23; others, 7) that responded to the 19-question survey developed by 15 hematologists with expertise in MDS was originally presented at the American Society of Hematology meeting in 2005,²⁰ Dr. Mufti presented an analysis based upon the 30 non-US respondents. Most centers (63% of respondents) reported using all three classification systems, and 23% used a combination of the IPSS with the FAB or WHO systems. However, 13% stated that their centers use only one of these classification systems, either the IPSS or the WHO. Of note, the use of a single system was more prevalent among the respondents outside of Europe (28.6% vs 8.7% within Europe), indicating not just a variability across the centers, but also a need to better communicate the ongoing advances in the treatment of patients with MDS. Furthermore, the wide range of preferences for treatments that this survey revealed (Table 2) points to an urgent need for establishing and disseminating evidence-based guidelines to assist clinicians in the effective matching of patient and disease characteristics with the available treatment options.

Further to the evolution of the IPSS, FAB, and WHO systems, a particular aspect that was discussed in the Education Sessions of the meeting by Aristotle Giagounidis, MD, of St. Johns Hospital in Duisburg, Germany, and Mario Cazzola, MD, of the University of Pavia School of Medicine, and of the IRCCS Policlinica S. Matteo in Pavia, Italy, was the latest advance that has been proposed for the establishment of the new WHO-based prognostic scoring system (WPSS; Table 3) and its improved ability to define the range of prognostic groups within patients with MDS.^{21,21}

The WHO system retains the refractory anemia (RA) and RA with ringed sideroblasts categories introduced in the FAB system. However, RA with excess blasts (RAEB) is divided into RAEB-1 and RAEB-2, based on blast percentage. New categories in the WHO system include refractory cytopenia with multilineage dysplasia (with or without ringed sideroblasts), MDS-unclassifiable, and del(5q) abnormalities.

Also, though not specifically discussed at this meeting, the standardized criteria for response assessment established in 2000 by the International Working Group (IWG) response criteria were recently updated.^{23,24} This classification originally arose as it became evident that MDS differs from other hematologic malignancies in its chronicity and the morbidity and mortality caused by chronic cytopenias, which are often seen without progression to AML. These criteria include measures of the alteration in the natural disease, hematologic improvement, cytogenetic response, and improvement in health-related quality of life. Therefore, the IWG response criteria were designed to reflect two sets of goals in the treatment of MDS: alleviation of disease-related complications to provide an improved quality of life and alteration of the natu-

Table 3. The Proposed WHO-based Prognostic Scoring System (WPSS)^{21,22}

	Points			
	0	1	2	3
WHO subtype	RA, RARS, del 5q	RCMD, RCMD-RS	RAEB-1	RAEB-2
Transfusion requirement Regular: ≥ 1 every 8 weeks over 4 months	None	Regular	-	-
Cytogenetic category Good: normal, del 5q, del 20q,-Y Int.: other anomalies Poor: complex (≥ 3), chromosome 7 anomalies	Good	Int.	Poor	-

Risk groups	Score
Very low	0
Low	1
Intermediate	2
High	3–4
Very high	5–6

RA = refractory anemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ringed sideroblasts; WHO = World Health Organization.

ral history of the disease. These criteria have also needed further modifications as knowledge of the molecular biology and cytogenetics of MDS improves.

Clinical Management and Quality of Life in the Treatment of Patients with MDS

Ulrich Germing, MD, and colleagues, of the Heinrich Heine University in Düsseldorf, presented a summary of the clinical characteristics and treatment of new patients with MDS handled in their tertiary referral center in 2005.²⁵ The aim was to determine the details behind the present-day treatment and clinical management of these patients (N=217) in a large academic institution. With a median age of 67 years, 93% were diagnosed with primary MDS, and the remaining with treatment-related MDS. Using IPSS criteria, the patients were classified as follows: low risk, 25%; intermediate-1, 36%; intermediate-2, 24%; high risk, 15%.

The range of treatments received by this patient cohort was essentially based upon either enrollment in clinical trials, or treatment with nonstandardized protocol regimens. In the former, these treatments included the histone deacetylase inhibitor valproic acid, a farnesyltransferase inhibitor, the DNA hypomethylating agents azacitidine (Vidaza, Pharmion) and decitabine (Dacogen,

MGI Pharma), the iron chelator deferasirox (ICL 670), the alkylating agent bendamustin, and allografting. The nonstandardized protocols included erythropoietin, granulocyte colony-stimulating factor, oral melphalan, thalidomide (Thalomid, Celgene), hydroxyurea, thioguanin, ATG plus cyclosporin A, imatinib mesylate (Gleevec, Novartis), desferrioxamine, danazol, low-dose azacitidine, and oral lenalidomide.

Thus, this analysis again highlights the wide variety of treatments that are at present being used in such tertiary referral centers, and the increasing need for central standardization of treatments for patients with MDS. Treatment decisions will hopefully soon be individually tailored to each patient according to their classification and prognostic scores, thanks to the expanding knowledge of the molecular basis for development of MDS and the new approaches that are being developed for its management and treatment.

Two analyses examining quality of life in patients with MDS were presented by the MDS Foundation. One arose from patient forum discussions,²⁶ and a similar study arose from health utility interviews with patients.²⁷ These analyses took the different approach of examining MDS as a disease from the patients' perspective. For the former study, Kathleen V. Heptinstall, RN, BSN, of the MDS Foundation in Crosswicks, New Jersey, and colleagues

reported on regular forums that were convened at European Centers of Excellence where patients, spouses, and caregivers got together to examine key issues relating to all aspects of the quality of life of patients living with MDS. The data presented were from the first six of these forums, held at centers in England, Scotland, and France, which included 66 patients with MDS and 101 caregivers.

Patients noted which treatment options they had received (Figure 1) and reported that the major impact on quality of life was fatigue, which diminished their ability to perform activities of daily living, work, and participation in social and family life. However, 44% indicated that they carried on with their normal life with only minor symptoms, with 18% having a normal life, 23% needing effort to engage in their normal life activities, and 9% taking care of themselves but not engaging in active work. Thus, patients requiring assistance either occasionally (3%) or to a considerable extent (3%) were by far in the minority. However, there was a general feeling of “loss of life control” from disruption of their lives due to both their MDS and the time required for disease management. This was well reflected by the number of treatments they were undergoing: bone marrow biopsy, 95%; second bone marrow biopsy, 73%; transfusions, 82%; iron chelation therapy, 20%; continued iron chelation therapy, 17% (66); antibiotics within the last month, 56% (37/66); hospitalized for treatment of infections, 36% (24/66); medical treatment for infection, 27%; active treatment for MDS, 33%; continued active treatment for MDS, 14%; and growth factor treatment, 44%.

Of note, the need for transfusions in tandem with iron chelation therapy was viewed as significantly affecting their quality of life, and as second only to fatigue, as a “necessary evil” to deal with fatigue. Furthermore, there was a general feeling of loss of emotional well being due to the “waiting for something to happen.” Indeed, potentially linked to this was their feeling that new drugs are not being made available quickly enough in Europe (65%). Thus, there is a continued need to lessen the patient disease burden by the reduction or elimination of transfusions, thereby decreasing the fatigue that is closely associated with the need for infusions and chelation therapy.

Allogeneic Transplantation

Allogeneic stem cell transplantation (ASCT) remains the only potentially curative therapeutic option for patients with MDS, and its use has been expanded beyond young patients.²⁸ Several aspects of ASCT in MDS patients were discussed by Dr. Cazzola in the educational sessions of the meeting.

Dr. Cazzola presented three reports concerning the decision-making side of ASCT, which is of particular

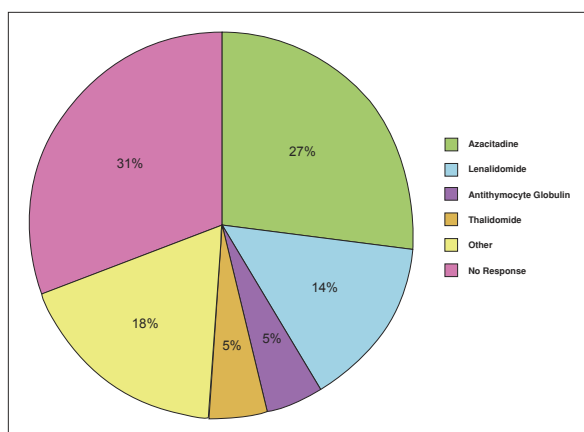


Figure 1. Prior experience with active treatments for patients with MDS according to European patient forums.²⁶

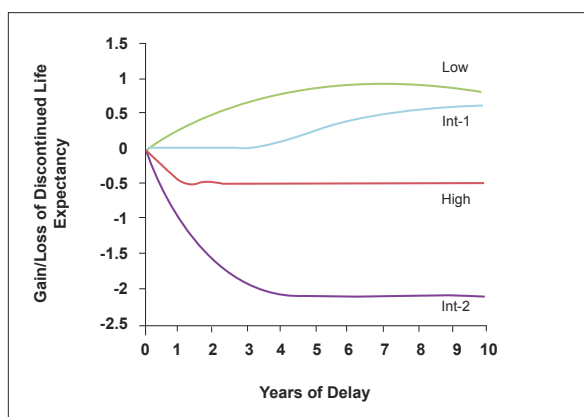


Figure 2. A decision analysis of the allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk MDS. This figure shows net benefit or loss of overall discounted life expectancy for the four IPSS risk groups.^{29,30}

Adapted from Cutler et al. *Blood*.²⁹

importance as the outcomes of these patients are highly dependent on their selection. The first report related to a decision analysis for allogeneic bone marrow transplant,²⁶ where according to normal practice the unfavorable prognostic variables that influence outcome after transplantation for MDS (older age, high marrow blast counts, marrow cytogenetics, use of induction chemotherapy prior to transplantation) all argue for early transplantation after diagnosis. However, as Dr. Cazzola indicated, this decision analysis demonstrated that life expectancy for patients with low- and intermediate-1-risk IPSS scores who have human leukocyte antigen (HLA)-identical siblings is higher when transplantation is delayed for some years but performed prior to development of AML (Figure 2). For IPSS intermediate-2 and high-risk

Table 4. Hematopoietic Cell Transplantation-specific Comorbidity Index^{30,31}

Comorbidity	Scores
Arrhythmia, cardiac, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric disturbance, hepatic (mild), obesity, infection	1
Rheumatologic, peptic ulcer, moderate/severe renal, moderate pulmonary	2
Prior solid tumor, heart valve disease, severe pulmonary, moderate/severe hepatic	3

Score	Nonrelapse Mortality		Survival	
	HR (95% CI)	2-year, %	HR (95% CI)	2-year, %
0	1	14	1.0	71
1–2	0.42 (0.8–2.7)	21	1.31 (0.8–2)	60
≥3	3.54 (2–6.3)	41	2.69 (1.6–4.1)	34

CI = confidence interval; HR = hazard ratio.

patients, transplantation soon after diagnosis remained predictive of better prognosis.³⁰

The second ASCT report highlighted by Dr. Cazzola also related to risk assessment prior to ASCT, with the recent definition of a hematopoietic cell transplantation (HCT)-specific comorbidity index.^{30,31} Here, a new tool was developed for identifying pretransplant comorbidities that can be used to predict outcome and for stratifying patients for HCT (Table 4). Finally, Dr. Cazzola considered the very recent retrospective comparison of reduced-intensity conditioning (RIC) and standard myeloablative conditioning (SMC) for ASCT using HLA-identical sibling donors in MDS.^{30,32} Although the 3-year probabilities of progression-free and overall survival were not significantly different between the two groups (SMC, 39% and 45%, respectively; RIC, 33% and 41%, respectively), the data were actually particularly encouraging due to the considerably greater proportion of older patients in the RIC group (>50 years: 73% vs 28% for SMC group; $P < .0001$), and their more adverse pretransplant variables.

Despite these encouraging developments, further improvements need to be made as only about one third of patients receiving allogeneic transplants are cured, and only about 8% of all patients with MDS are both eligible and have a donor.

Modulation of the Immune System: The Benefit of Lenalidomide in the Treatment of MDS

As detailed in recent reviews of the evolution of thalidomide and its immunomodulatory drug derivatives,^{33,34} although thalidomide was originally synthesized in 1954, it is under further active investigation even today, despite its teratogenic toxicity, which resulted in market withdrawal in 1961 from its indication during pregnancy.

In 1965 thalidomide began to be investigated in other settings, showing efficacy in the treatment of erythema nodosum leprosum, a potentially life-threatening inflammatory complication of lepromatous leprosy, leading to further investigations into its immunomodulatory and anti-inflammatory actions.

Among the many other disease types for which thalidomide has been investigated, its efficacy in multiple myeloma led to the suggestion for its use in MDS.^{33–35} Here, the primary mechanisms of action reported for thalidomide include: (i) inhibition of the synthesis of monocyte-derived tumor necrosis factor (TNF)- α , which explains many of its anti-inflammatory actions; (ii) inhibition of angiogenesis, a crucial stage in the growth and metastasis of solid tumors; and (iii) costimulation of T cells that have been partially activated by the T-cell receptor, facilitating naive T-cell activation and their subsequent generation of an antigen-specific effector response. Very recently, a phase II study evaluated thalidomide in combination with the topoisomerase I inhibitor topotecan for the treatment of MDS,³⁶ and another study combined thalidomide with erythropoietin for the treatment of anemia in MDS patients.³⁷

However, it was thalidomide's efficacy in patients with multiple myeloma that led to its further development and the synthesis of two analogs, CC-4047 and CC-5013 (lenalidomide), which are up to 50,000 times more potent than thalidomide at inhibiting TNF- α . These compounds have also been confirmed as antiangiogenic agents, and shown to be more potent than thalidomide in the costimulation of T cells; they also trigger phosphorylation of CD28 and enhance the activity of the AP-1 transcription factor.^{33,35}

The results of an open-label, single-center trial evaluating lenalidomide in MDS patients with transfusion-dependent or symptomatic anemia were reported by List

and colleagues in 2005.³⁸ Of the 43 evaluable patients, 56% experienced an IWG-defined erythroid response and 20 of 32 transfusion-dependent patients (63%) achieved independence from transfusion. The response rate was highest among patients with the del(5q31.1) MDS mutation (n=12)—83% had a cytogenetic response and 9 patients achieved a complete cytogenetic remission—and patients with lower prognostic risk. After a median follow-up of 81 weeks, the median duration of transfusion independence had not been reached. Neutropenia and thrombocytopenia were the most common side effects, and necessitated dose reduction or interruption in 25 patients.

These encouraging results led to two additional phase II trials investigating possible differences in the safety and efficacy of lenalidomide in lower-risk MDS patients with (MDS-003; N=148) or without (MDS-002; N=215) an associated del(5q) abnormality. Dr. Giagounidis, on behalf of the study group, gave a presentation from the two trials as of September 2005.³⁹

Following a 16-week prestudy for transfusion documentation of the eligible patients, registration was set at week 0, with response assessment at week 24. Lenalidomide was administered at either 10 mg orally for 21 days on and 7 days off, or 10 mg/day orally for the duration of the trial, with the responders continuing on treatment. The primary endpoint in both studies was transfusion independence, and their secondary endpoints were cytogenetic and pathologic responses.

There were no significant differences in baseline characteristics between the patients with non-del(5q) MDS (MDS-002) and del(5q) MDS (MDS-003), except for the mutation itself and hence the expected reversal of the 2:1 male:female ratio from MDS-002 to MDS-003; similarly, central review of the IPSS/FAB classifications showed no significant differences. The first major difference between these non-del(5q) and del(5q) trials was in the comparison of the erythroid response of the intention-to-treat populations across the trials. Here, transfusion independence occurred in 27% (56/215; 95% confidence interval [CI], 21–33) and 67% (97/148; 95% CI, 58–74), respectively. Inclusion of the minor erythroid response ($\geq 50\%$ reduction in transfusion dependence; 17% and 9%, respectively) thus brought the overall erythroid responses to 43% (93/215; 95% CI, 37–50) and 76% (113/148; 95% CI, 68–83), amply illustrating the added benefit of this treatment in the patients with del(5q) MDS. The median time to response, however, was the same for the two trials at 4.6 weeks.

Dr. Giagounidis also highlighted how effective lenalidomide treatment was in terms of hemoglobin levels, with a direct comparison of the nonresponders and responders in the MDS-003 study. The baseline hemoglo-

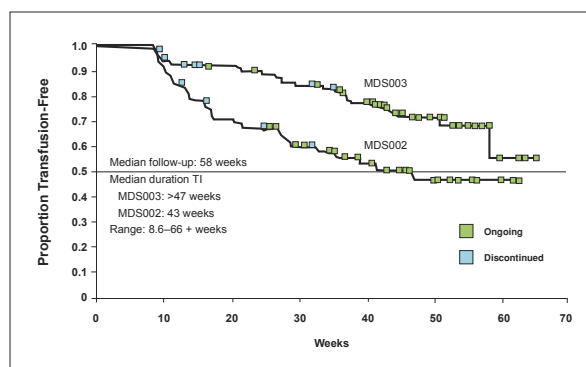


Figure 3. Transfusion-free duration for lenalidomide-responders of patients in the MDS-002 and MDS-003 studies (N=97).³⁹

bin across all patients was 7.8 g/dL (95% CI, 5.3–10.4); although this did not change in the nonresponders, in the lenalidomide responders a sharp increase in hemoglobin levels was seen around the second cycle of treatment. By the third cycle this was within the National Comprehensive Cancer Network guidelines,⁸ with maintenance of a maximum hemoglobin level of 13.4 g/dL (95% CI, 9.2–18.6) throughout the use of lenalidomide, as documented through 18 treatment cycles. These responders thus showed a significant median hemoglobin increase of 5.4 g/dL (95% CI, 1.1–11.4).

A direct comparison of the differences in response according to the proportion of transfusion-free patients in MDS-002 and MDS-003 (Figure 3) further illustrates the selective benefits of lenalidomide treatment for patients with del(5q) MDS. With a median follow-up of 58 weeks, the mean duration of patient transfusion independence was 43 weeks for MDS-002 and had not been reached for MDS-003 (>47 weeks).³⁹

There was also a beneficial marrow histologic response seen in MDS-003: of the 106 evaluable patients, 36% showed a complete marrow histologic response.³⁹ Dr. Giagounidis then detailed the transfusion independence according to the baseline cytogenetics for these patients. Indeed, this analysis was of particular interest as potentially the transfusion independence could be dependent upon the cytogenetic complexity of the patients at baseline. However, a comparison of the transfusion independence within each cytogenetic subgroup showed no significant differences at this level of population. Similarly, when the cytogenetic responses of the eligible patients in MDS-003 were compared according to their baseline cytogenetic complexities, no significant differences were seen. Thus, both transfusion independence and cytogenetic response were independent of karyotype complexity and del(5q) breakpoint.

Table 5. Characteristics of Response to Lenalidomide in MDS-003

Group	Response	Patients, %
1	Rapid response to treatment and no relevant cytopenias. Usually develops cytogenetic and hematologic remission. Some dose reductions due to nonhematologic toxicities	10
2	Hematologic response after dose reduction with cytopenia. Dose-limiting cytopenias at 7–96 days. Higher incidence of grade 4 neutropenia. Life-threatening infections in 6%. Rapid recovery (1–4 weeks) after interruption of therapy	50
3	Response lost but second remission achieved. Potential benefit from ≥ 1 mo drug holiday or interruption and resuming therapy at higher dose. Second response generally shorter than first	10
4	Long-term transfusion independence after discontinuation of therapy	1 patient
5	No response	30

Dr. Giagounidis finally considered the direct comparison of the most common drug-related grade 3/4 adverse events across these two trials. Of particular note, although it is known that lenalidomide treatment can lead to neutropenia and thrombocytopenia, the levels were much higher in the patients with del(5q) MDS (59% and 51%, respectively) than in the non-del(5q) group (24.1% and 19.5%, respectively). For the other grade 3/4 adverse events there were no significant differences across these two patient groups, although Dr. Giagounidis indicated that some of the grade 1/2 adverse events, such as diarrhea, dry skin, pruritis, and muscle cramps, did require treatment.

In summarizing the study conclusions for each of these two trials, Dr. Giagounidis noted that among the patients with non-del(5q) MDS, a total of 43% achieved a reduction or elimination of their transfusion burden, with hemoglobin levels of responders returning to normal. Thus, as well as being an orally dosed agent with manageable toxicities, lenalidomide use resulted in a rate of transfusion independence in this patient group comparable to that seen with other agents used to treat lower-risk MDS.

For the patients with del(5q) MDS, lenalidomide showed significant clinical benefit, with durable resolu-

tion of refractory anemia, significant rise in hemoglobin levels, cytogenetic responses and remission that were independent of the karyotype complexity and del(5q) breakpoint, marrow normalization and improvement, and well-characterized and manageable adverse events. These findings led to the recent approval by the US Food and Drug Administration (FDA) for the use of lenalidomide in patients with anemia due to low- or intermediate-1–risk transfusion-dependent MDS associated with a del(5q) abnormality with or without additional chromosomal abnormalities.

Patterns of Response for Lenalidomide in Patients with del(5q) MDS

In an interesting follow-up poster presented at the meeting by Dr. Giagounidis and colleagues, the patterns of patient response within the MDS-003 trial were analyzed in more detail.⁴⁰ This analysis has the potential to be of particular use to the physician, as this treatment approach could safely induce remissions in patients with del(5q) MDS. They described five specific groups according to the management characteristics of their responses to lenalidomide (Table 5):

Group 1: Uncomplicated responder. Seen in about 10% of patients, they showed rapid response (within 3 weeks) to treatment and no relevant cytopenias. These patients usually developed long-term hematologic and cytogenetic remission; some needed dose reductions due to nonhematologic toxicities.

Group 2: Typical responders. Some 50% of “typical responders” achieved a hematologic response after dose reduction with cytopenia. They developed dose-limiting cytopenias after 7–96 days and were at particular risk of neutropenia, which regularly occurred at grade 4. Weekly blood tests should be mandatory in these patients to prevent serious and life-threatening infections, which were seen in 6%. Serious bleeding events never occurred, however, because lenalidomide treatment was interrupted when platelet counts fell below 50,000/ μ L. Cytopenias appear to be indicative of long-term remission when baseline values for neutrophils and platelets are normal or near normal. Regeneration is prompt (usually 1–4 weeks) after interruption of therapy.

Group 3: Intermittent responders. Around 10% of patients lost their response, although they could achieve a second remission. Some appeared to benefit from a “drug holiday” of 1 to several months, while others achieved a second response after interruption and when restarted at a higher lenalidomide dose than their previous maintenance dose. Bone marrow examination in patients with neutropenia can be misleading, as an increased medullary

blast count will usually return to normal. Their second response is usually shorter than their first.

Group 4: Long-term transfusion independence after discontinuation of therapy. This was seen in 1 patient, where long-term (>15 months) transfusion independence was seen after discontinuation of therapy, despite not showing an objective response during the 12-month treatment with lenalidomide.

Group 5: Nonresponders. About 30% of patients with del(5q) MDS will not respond to lenalidomide therapy. This appears to be irrespective of whether they present with isolated del(5q) with less than 5% blasts (5q- syndrome) or with another subtype of del(5q) MDS.

Of further interest, the investigators noted that of 3 patients with del(5q) MDS who received lenalidomide for only short durations (<8 weeks), 2 achieved long-term (>18 months) transfusion independence despite the persistence of the del(5q) abnormality in their bone marrow.

The introduction of lenalidomide and its subsequent approval by the FDA represents a great advance in the treatment of transfusion-dependent anemia in patients with del(5q) MDS. However, although the data reported by Dr. Giagounidis indicated that lenalidomide showed no further selectivity within these patients, as stated recently by Galili and Raza,³⁵ “it is important to more precisely define the subset of patients who are potential responders to lenalidomide so that undue toxicity can be avoided for those who have little chance of benefiting” treatment with this agent.

Clinical Versus Cytogenetic Response

As indicated above, the ability to selectively target the del(5q) cytogenetic abnormality with lenalidomide did not show any selectivity within the various del(5q) “diseases” (del[5q] alone ± blasts; del[5q] + other chromosomal abnormalities ± blasts); this highlights the need for a definition of cytogenetic response and determination of how the many chromosomal abnormalities associated with MDS affect patient treatment and survival. Such a “prognosis versus cytogenetics” relationship was indicated in a poster presentation by Dr. Giagounidis.⁴⁰ Approximately 15% of patients with MDS display a del(5q) abnormality, which is considered for purposes of lenalidomide administration a single “disease”; however, although these 5q deletions appear cytogenetically similar, they are actually highly variable in molecular terms.⁴¹ Similarly, very recent data indicate that a number of the other single-change chromosomal aberrations may present distinct disease entities themselves.^{42,43}

Thus, with MDS it is important to define the potential relationships between clinical and cytogenetic response to ascertain the appropriate patient treatment. To help clarify this situation with regard to the use of the DNA hypomethylating agent decitabine, which targets epigenetic defects in cancer with the aim of normalizing gene expression, Kantarjian and colleagues presented an analysis of the cytogenetic responses from their recently reported multicenter randomized, phase III trial of decitabine treatment versus supportive care (SC) in patients with MDS.^{44,45}

In this study, 170 eligible patients were stratified according to IPSS classification, prior chemotherapy, and study center, and randomized to receive either decitabine plus SC (n=89) or just SC (n=81; antibiotics, growth factors, and/or transfusions). As they have reported, using IWG response criteria, the decitabine group showed an overall response rate of 17% (15/89) (9% complete response [CR] and 8% PR) and 13% (12/89) hematologic improvement, as compared to the no responses and 7% (6/81) hematologic improvement seen with SC alone.

To determine how this treatment relates to patient cytogenetics, and thus potentially for the definition of a “target” patient subgroup for decitabine treatment, Dr. Kantarjian said that of the 95% of patients who had a cytogenetic analysis of their bone marrow samples at study entry, a subset of these (decitabine, n=27; SC, n=21) who had abnormal cytogenetics at baseline consented to follow-up cytogenetic evaluations at 3 to 6 month intervals. Overall, abnormal karyotypes were identified in 58% (49/84) of the decitabine group and 57% (43/75) of the SC arm, with the most common abnormalities being del(5q), del(7q), trisomy 8, and complex (>2) abnormalities. Following decitabine treatment, the responses seen (CR + PR) showed no significant differences according to patient cytogenetics (Table 6); however, when analyzed according to the relationship between the cytogenetics and time to AML or death, a selective protective effect of decitabine treatment over SC was indeed seen. Thus, while the SC arm demonstrated a progressive decrease in time to AML or death (del[7q] > diploid > complex > del[5q] > trisomy 8), there were no significant differences across these groups following decitabine treatment.

Finally, while acknowledging the relatively small numbers here, Dr. Kantarjian noted that with decitabine treatment all of the clinical responses (CR and PR) to decitabine were cytogenetic, although 3 patients receiving this agent treatment showed a cytogenetic response that was not viewed as a clinical response according to the IWG criteria. He also noted three particular points of interest: (i) all of the cytogenetic responses were already apparent at the first testing at 3–9 months (median, 4.5 months); (ii) two of the patients in the SC arm also

Table 6. Responses to Decitabine Treatment by Cytogenetics^{44,45}

Cytogenetics	Response to DAC (CR or PR)
Normal	5/35 (14%)
Complex	4/20 (20%)
Del 7/7q	4/20 (20%)
Del 5/5q	3/19 (16%)
Trisomy 8	3/15 (20%)
Del 20q	2/12 (17%)

CR = complete response; DAC = decitabine ; PR = partial response.

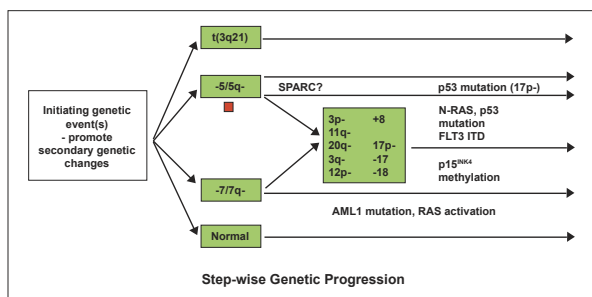


Figure 4. Proposed model for molecular pathogenesis of MDS.^{46,47}

showed major cytogenetic responses; and (iii) of the three decitabine-treated patients who reached complete cytogenetic response and then later relapsed, this relapse was associated with similar cytogenetic abnormalities to those that these patients had at study entry. Of importance, this final observation indicated that decitabine treatment itself did not induce any chromosomal instabilities. Thus Dr. Kantarjian concluded that in these patients with MDS who were treated with decitabine and supportive care, this DNA hypomethylating agent does indeed induce clinical remission by the clearing of the malignant clone.

However, the mechanisms behind this clonal elimination remain to be determined, and future cytogenetics-based treatments will need to take into account the stepwise genetic progression of the proposed model for the molecular pathogenesis of MDS, as presented in the Educational Session by Jacqueline Boulwood, PhD, of the John Radcliffe Hospital, University of Oxford, Oxford, UK (Figure 4).^{46,47} Of note, these analyses are now being taken forward from the initiating genetic events that define the cytogenetic background of patients with MDS to consider the resultant gene changes that are now becoming better associated to specific cytogenetic conditions.

As a follow-up of the recent phase II study of the sulfonylhydrazine alkylating agent VNP40101M (cloretazine, Vion) in the treatment of patients with AML,⁴⁸

Verena Karsten, PhD, of Vion Pharmaceuticals Inc., presented an extended dataset from this recently completed CLI-033, multicenter, phase II trial that included a total of 109 patients with de novo AML (n=44), secondary AML (n=45), and high-risk MDS (n=15).⁴⁹

This novel alkylating agent has recently been shown to have significant antileukemic activity both in vitro and in vivo,⁵⁰⁻⁵² with its proposed mechanism of action being activation and alkylation of the O6 position of guanine, resulting in crosslinking of DNA.^{53,54} Early phase I studies showed dose-limiting toxicities of VNP40101M on myelosuppression in both solid tumor and hematologic trials, thus indicating potential for this novel agent in hematologic malignancies. The treatment here consisted of VNP40101M 600 mg/m² administered intravenously (IV) as a single infusion over 30–60 minutes on day 1, accompanied by hydroxyurea 30 mg/kg twice daily for 6 days, starting on day 1. A second round of induction was included for patients with improved bone marrow, with consolidation at the physicians' discretion with VNP40101M 400 mg/m² IV as a single dose.

The overall clinical response rates within each disease group were 50% for de novo AML (CR/PR, 20/2 patients), 11% for secondary AML (5/0) and 40% for high-risk MDS (4/2). Despite the relatively low patient numbers, particularly in the high-risk MDS group, the initial analysis of the total patient demographics also included their classification according to cytogenetics, as favorable (n=0), intermediate (normal, +8, -Y; n=56) or unfavorable (n=46), and according to their Eastern Cooperative Oncology Group performance status (ECOG PS); Dr. Karsten indicated the breakdown of the response data accordingly.

The clinical response according to cytogenetic risk demonstrated equivalent efficacy for VNP40101M for de novo AML, with a higher response for the patients with intermediate- versus high-risk MDS (50% vs 29%); VNP40101M proved less effective against secondary AML (19% vs 4%, respectively). For ECOG PS, there was little difference across these subgroups, and any potential significance will need to await data from a further phase II trial that has the express design of focusing on the more beneficial results seen here for patients with de novo AML. Dr. Karsten also noted that this treatment was well tolerated across all patient subgroups, with the expected myelosuppression and minimal nonhematologic toxicity.

Two Thousand Years of Use, and More: The Arsenicals

Gail J. Roboz, MD, of Weill Medical College of Cornell University, New York, NY, USA, presented data from a study of the combination of arsenic trioxide (ATO) and low-dose cytarabine (ara-C) in the treatment of patients

with advanced MDS and with AML.⁵⁵ The use of two-agent (or more) combinations based around ara-C has very recently expanded with respect to MDS, with a variety of agents being tested, including topotecan, idarubicin or fludarabine,⁵⁶ triapine,⁵⁷ and the histone deacetylase inhibitor sodium phenylbutyrate (Buphenyl, Medics).⁵⁸⁻⁶⁰ Similarly, despite earlier reports having shown little or no efficacy for ATO in patients newly diagnosed and/or relapsed for AML, two very recent reports that did show moderate activity of ATO as a single agent in patients with MDS^{61,62} both highlighted the need for therapeutic regimens combining ATO with other agents to improve the clinical efficacy of ATO.

Dr. Roboz indicated that many small phase II studies over the last 25 years have shown CR rates of only around 20% with ara-C, which were also generally only of short duration. As similar rates have also been seen using low ara-C doses (10–20 mg/m² subcutaneous BID), Dr. Roboz and colleagues decided to combine low-dose ara-C with ATO. She also noted that the mechanisms of action of ATO are known to be wide, and to include the activation of apoptosis, the inhibition of angiogenesis, and the suppression of cellular proliferation.

This single institution, phase I/II trial included 99 patients enrolled to date who were over 60 years of age with newly diagnosed AML (n=63), or IPSS int-2 or high-risk MDS (n=36). They used an initial dose escalation of ara-C from 5 mg/m² to 10 mg/m² subcutaneously twice daily in combination with ATO 0.25 mg/kg IV on days 1–5 and 8–12; the data reported were from the ara-C target dose as no remission was seen in patients treated with the lower dose. Following CR, there was one identical consolidation cycle given, and then maintenance with 5 days of ara-C 10 mg/m² twice daily and 2 days of ATO 0.25 mg/kg monthly. During treatment with this regimen, close attention was paid to patient electrolytes and electrocardiograms, with supportive care of transfusions and antibiotics as needed.

For patients with MDS, there was an 18% (5/28) CR with a median duration of 3 months, that remained ongoing in 3 patients; 60% (3/5) of these CRs required two or three cycles of treatment. Stable disease was seen in 21% (6/28) and failure in 46% (13/28), with MHI-E and MHI-P at 7% (2/28) and 11% (3/28), respectively. For the patients with AML, the responses were: CR, 34% (18/53); overall remission rate, 40% (21/53); no response, 13% (7/53); progressive disease, 36% (9/53); and IM, 9% (5/53).

Nonhematologic toxicities were mainly grade 1/2; the major grade 3/4 toxicities were pleural effusion (18%), sepsis (15%), bleeding (14%) and increased alanine aminotransferase levels (11%). Cardiac toxicities were closely monitored due to the use of ATO; here, there were few

QTc and QT prolongations that required interruption of therapy (8% and 2%, respectively); prolongations that did not require interruption of therapy were 41% and 6%, respectively. None of these QTc and QT prolongations had clinical manifestations; however, 2 patients did have short, asymptomatic runs of torsade de pointes after ATO therapy had been completed and while telemetry was being used for other clinical indications. Grade 3/4 myelosuppression was seen in all patients, with neutropenic fever in 61% and 80% of the MDS and AML groups, respectively.

Based on the findings, Dr. Roboz concluded that it is indeed feasible and effective to combine low-dose ara-C with ATO in these poor-prognosis, older patients with MDS and AML. The favorable extramedullary toxicity profile compared to conventional induction therapy, and a notable absence of significant nausea, emesis, mucositis, and diarrhea add to the potential appeal of this approach. Similarly, careful monitoring meant that cardiac arrhythmia was not a clinically significant problem. Several patients were able to proceed to nonmyeloablative stem cell transplantation with no obvious transplant-related complications.

For patients with MDS, Dr. Roboz noted that although they represented a small group, they did obtain a higher CR than some others that have been reported, both for low-dose ara-C alone and for ara-C in combination. To investigate this regimen further, they are now going forward with the development of a phase III randomized trial of ATO plus low-dose ara-C in direct comparison with low-dose ara-C alone.

Future Directions

Treatment-related trends and understanding of MDS are at present being greatly improved through numerous recent and ongoing studies, many aspects of which were presented at the 11th Congress of the European Hematology Association. However, even though these new therapeutic options already demonstrate a much improved prognosis for specific subgroups of patients with MDS, many aspects remain to be expanded upon if physicians are to be able to provide the necessary wide framework and correct choice of therapies for patients.

Thus, a new level of understanding of MDS is necessary to allow us to determine how patients' clinical and cytogenetic diversity can be matched to the diversity of the targets and effects of the expanding array of drugs now available against MDS, both in terms of symptoms and disease progression. This will necessitate the coupling of more mechanistic approaches to drug activity with a better understanding of the meaning of the wide and varied cytogenetic problems that are associated with MDS.

Finally, the expanding knowledge of the treatment and inner complexities of MDS must also be paralleled by its dissemination to the real-world clinic, so that these benefits can be made available to all who need them.

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