

In this issue, we review current treatment approaches for patients with myelodysplastic syndrome (MDS) at M. D. Anderson Cancer Center. Over the last 3 years, several significant advances have occurred in MDS. These include the approval by the FDA of 3 different treatments: 5-azacitidine (Vidaza), lenalidomide (Revlimid), and 5-aza-2'-deoxycytidine (Dacogen). Although of great significance, complete remissions with these agents are infrequent, and some of these therapies target very specific subsets of patients (i.e. lenalidomide for those with alterations of chromosome 5). Therefore, there is a need to continue to develop new therapies for patients with MDS and to improve current available therapies. Together with advances in therapy, we have also witnessed advances in our understanding of supportive care measures in MDS and in the development of new classification systems. All of these should allow the development of targeted therapeutic approaches for specific subsets of patients with MDS. We are conducting research in these areas and have summarized them below.

## Classification Systems in MDS

The most difficult problems in MDS are its morphological diagnosis, access to cytogenetic testing, and therefore application of the different classification systems. These include the FAB<sup>1</sup> and WHO<sup>2</sup> classifications and the most clinically relevant IPSS<sup>3</sup> score. This latter scoring system incorporates percentage of blasts, number of cytopenias and chromosomal alterations to predict overall survival and probability of transformation to AML based on the age of the patient. Despite being more comprehensive and dynamic than the FAB and WHO classifications, it has become apparent that the IPSS has limitations in

predicting prognosis of patients with lower-risk MDS. Also several groups have now presented data with more refined cytogenetic classifications<sup>4</sup>. Based on these, we are currently developing a new classification system for patients with lower risk disease. To do this we studied close to 900 patients referred to our center over the last 25 years with low or intermediate-1 MDS (by the IPSS score) that had not received therapy. The first important observation was that 10% of patients eventually transformed to AML. This indicates the need to treat patients with lower-risk MDS. Second, we have developed a scoring system that allows us to separate these patients with lower risk MDS into three subgroups (Figure 1): 80 % of patients will survive less than 2 years after referral without therapy. This data is of great importance as many of these patients are currently observed and not treated. The validation of this data would provide a frame work for introducing new agents in MDS.

### *In This Issue*

- 1 Classification Systems in MDS**
- 2 Epidemiology of MDS**
- 2 Advances in Supportive Case**
- 2 Specific Patient Situations**
- 3 New Treatment Strategies**
- 4 Summary**

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## Epidemiology of MDS

Until recently, we did not have access to SEER data in MDS. This data is now starting to be developed and is confirming that MDS differentially affects older patients. As the current generation's age and life expectation

lengthens, MDS may become a significant health issue world wide. This also emphasizes the need to develop therapies for older patients not candidates for intensive chemotherapy or bone marrow transplantation.

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## Advances in Supportive Care

Until recently most patients with MDS, particularly those with lower risk received only supportive care including platelet and red blood cell transfusions, and more recently the use of growth factors. Several new developments have emerged recently. First, the discovery that the combination of erythropoietin and neupogen not only has a synergistic effect on response<sup>5</sup>, but also may improve survival in patients with lower risk disease<sup>6</sup>. Another important issue relates to iron accumulation and its consequences in MDS. It is now emerging that iron disposition has an effect on the natural history of the disease and iron chelation may also improve survival<sup>7</sup>. We

are currently studying several of these issues in MDS.

One of the most difficult problems in MDS is management of thrombocytopenia. Use of prior platelet growth factors has been associated with poor response rates and toxicities. We are now exploring the activity of the thrombomimetic agent AMG531 (protocol 2005-0577) in patients with thrombocytopenia with encouraging results.

Other studies at our center include studies with the oral iron chelation agents in MDS, the role of combination growth factors in MDS, and the use of a new formulation of ATG for patients with aplastic anemia and lower risk MDS.

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## Specific Patient Situations

The understanding of specific alterations is allowing the development of targeted clinical trials in MDS. Several MDACC studies meet this criteria:

**2006-0293:** The activity of lenalidomide is well accepted in patients with low and intermediate-1 risk MDS, but it is not known whether it is also active in patients with higher risk disease and a chromosome 5 alteration. This is being tested now in patients with intermediate-2 or high-risk scores. The results of this study will have implications for the treatment of patients with chromosome 5 and AML or high-risk MDS.

**2005-0913:** Deregulated immune responses may have a role in the pathogenesis of MDS. Pilot studies by MDACC investigators indicated that a vaccine against PR1 in HLA-A2 patients had activity in patients with advanced leukemia. We are now studying the activity of these vaccines in

patients with low or intermediate-1 risk disease. This study just opened at M. D. Anderson Cancer Center and offers the possibility of potentially active therapy with minimal toxicity.

**2005-0115:** Patients with hypocellular MDS constitute a distinct group of patients for whom treatment with ATG may be beneficial. We are conducting a study combining rabbit ATG, cyclosporine, and growth factors for patients with aplastic anemia or hypocellular MDS. This is a group of patients whose treatment is especially complex.

**2004-0468:** Finally, it is not known whether there is cross-resistance between the two hypomethylating agents vidaza and dacogen. We are conducting a study with dacogen for patients that have failed vidaza therapy that will provide insights into this important question.

## New Treatment Strategies

We divide our patients based on IPSS category. A complete list of available studies is shown in Figure 2.

### Low-Risk:

Treatment strategies for this group of patients include the PR1 vaccine, the combination of ATG and cyclosporine, the use of AMG531 (for patients with low platelets), deferasirox, and the combination of growth factors. One potentially very interesting compound is GX15-070ms, a small molecule Bcl-2 inhibitor. This agent has shown clinical activity in patients with CLL and MDS. Deregulated apoptosis is a hallmark of MDS and therefore the rationale for its approach.

### INTERMEDIATE-1:

In this group of patients, we are studying several different strategies. Together with the PR1 vaccine, we are using an oral or IV formulation of clofarabine at lower doses. Clofarabine, which is approved for children and relapsed ALL, also has activity in AML and higher-risk MDS. A new lower dose of clofarabine may result in an active and safe therapy for this group of patients. Third, prior studies have indicated that the combination of hypomethylating agent with a histone deacetylase inhibitor (HDAC) has significant activity in AML and MDS<sup>8</sup>. Two studies are targeting this strategy in MDS. This includes a randomized study of decitabine with or without valproic acid, and the combination of vidaza with MGCD0103. The aim of the first study is to confirm that valproic acid adds to the activity of decitabine. This is an important study that will serve as the basis for other more powerful HDAC inhibitors. MGCD0103 is a new HDAC inhibitor with single agent activity in AML. It belongs to a new group of selective HDAC inhibitors. The combination of these two agents was reported to have a 30% response rate in patients with relapsed AML<sup>9</sup>.

### INTERMEDIATE-2/High Risk:

Together with the clofarabine, dacogen ± valproic acid and vidaza + MGCD0103 studies described above, two other studies are available:

the study of lenalidomide in patients with chromosome 5 alterations and a phase 2 study of single agent MGCD0103.

### CMML

CMML is considered a distinct pathologic entity. For patients with non-proliferative disease, three specific treatment opportunities are available: 1) study of BMS-354825 (dasatinib); 2) phase 1 of Bay-43-9006 (sorafenib) and 3) a study of Velcade. The first two agents are multikinase inhibitors. Initial experience indicated activity in this setting.

### Planned Studies

Several studies are to be opened to patient accrual in the next few months. This includes:

1. Oral Vidaza. A new formulation of oral Vidaza is being developed. An ongoing study at M.D. Anderson Cancer Center is demonstrating that oral vidaza can be absorbed. Based on this data, we are planning a phase 1 study of oral vidaza for patients with MDS. This could result in the development of the first oral hypomethylating agent with the possibility of extended chronic oral use of therapy in MDS and potentially a breakthrough for these patients.
2. Single agent vorinostat for lower-risk MDS. Vorinostat (SAHA) is the first HDAC inhibitor approved for patients with cutaneous lymphoma. In an initial study vorinostat had activity in AML. Data from Europe has indicated that valproic acid (a neuroleptic with weak HDAC inhibitory activity) has moderate activity in MDS. If this concept is correct, the use of vorinostat may have significant activity.
3. Low dose subcutaneous decitabine. Decitabine has significant activity in intermediate-1 and above MDS, but its activity and toxicity profile is unknown in patients with lower-risk disease, in particular those with low risk. We have developed a new subcutaneous schedule of more weekly administration studies.

Other studies will include the use of LBH598, either alone or in combination for patients with MDS. LBH is a very potent HDAC inhibitor.

## Summary

The Leukemia Department at M. D. Anderson Cancer Center is committed to research into the biology of MDS and its clinical strategies. A list of front line and subsequent studies can be seen in Figure 2 and Figure 3. Together with these therapeutic trials, significant effort in the molecular biology of MDS is being studied by several investigators under the umbrella of the NIH

funded MDS P01 grant (E. Estey, principal investigator).

If you are interested in more information regarding any of the information provided here please do not hesitate to contact Guillermo Garcia-Manero, Chief, Section of MDS or Hagop Kantarjian, Chairman, Department of Leukemia, or any of the Leukemia physicians listed below.

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1. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982;51:189-199.
2. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. *Ann Oncol.* 1999;10:1419-1432.
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Figure 1

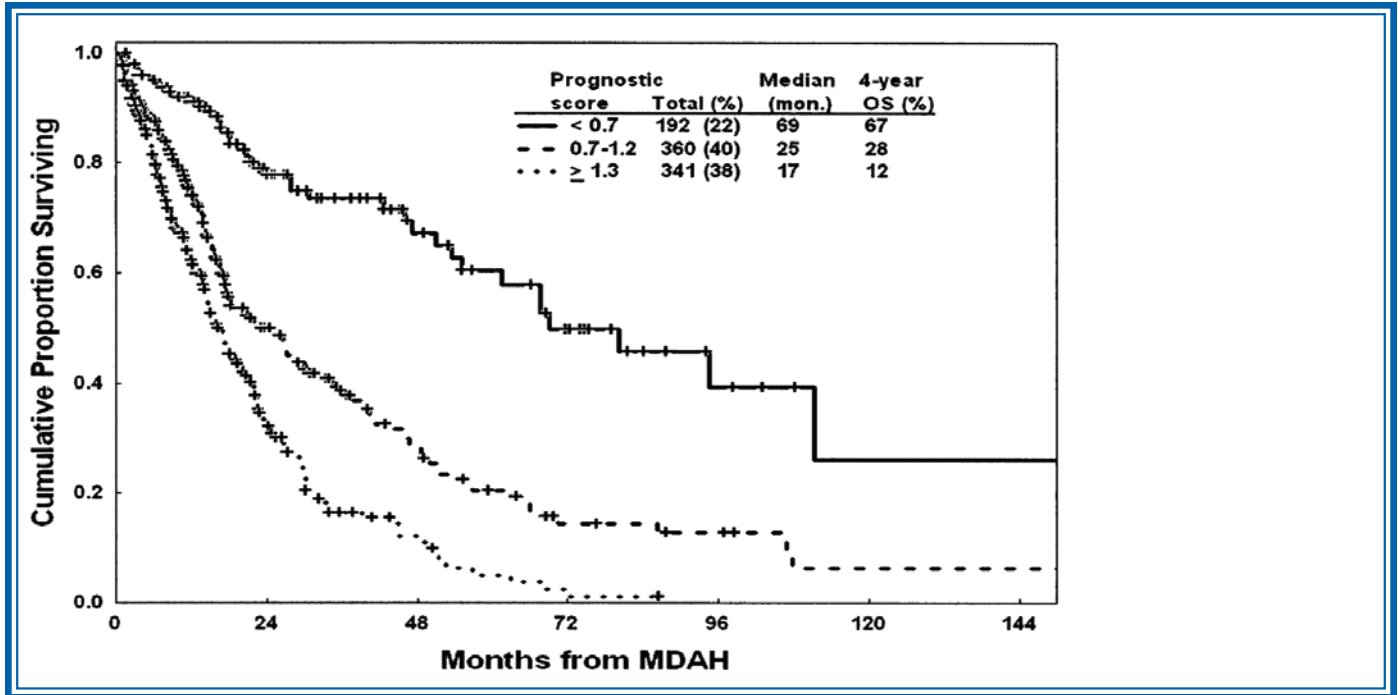


Figure 2

## MDS Treatment Priorities

### Specific Situations

- HLA A2 Positive – Low/Int-1 – PR1 Peptide Vaccine (Estey) (2005-0913)
- Hypocellular MDS – Thymoglobulin + CSA (Ravandi) (2005-0115)
- Aza failure – LD Decitabine (Kantarjian) (2004-0468)

### Low Risk

1. Ph II Proteinase 3 PR1 Peptide Vaccine (Estey) (2005-0913)
2. Ph II (GX15-070MS) (Borthakur) (2006-0688)
3. Thymoglobulin + CSA in aplastic anemia and hypoplastic MDS (Ravandi) (2005-0115)
4. AMG 531 (Kantarjian) (2005-0577) (Platelet transfusion dependent)
5. Cytokine Immunotherapy (Borthakur) (2004-0253)

### IPSS Int-1

1. Ph II Proteinase 3 PR1 Peptide Vaccine (Estey) (2005-0913)
2. Ph II LD DAC +/- VA (Issa) (2006-0686)
3. Ph II Oral Clofarabine (2005-0536) OR 3. IV Clofarabine (2005-0535) (Kantarjian)
4. Ph I/II MGCD0103 (MG-0103) + Aza (Garcia-Manero) (2005-0659)

### IPSS int-2 or high

1. Ph II LD DAC +/- VA (Issa) (2006-0686)
2. Ph II Oral Clofarabine (2005-0536) OR
3. IV Clofarabine (2005-0535) (Kantarjian)
4. Ph I/II MGCD0103 (MG-0103) + Aza (Garcia-Manero) (2005-0659)
5. Ph II MGCD0103 (MG-0103) (Garcia-Manero) (2006-0474)

### Other Studies

- Azacitidine (PK study) (Garcia-Manero) (2006-0784)
- Examination of PNH, by level of CD59 (EXPLORE) (Ravandi) (2006-0939)
- AMG 531 in patients receiving Lenalidomide (Kantarjian) (2006-0796)
- AMG 531 in patients receiving Hypomethylating Agents (Kantarjian) (2006-0722)

Figure 3

Protocol	Protocol #	PI
Ph I HuM195/rGel	DM98-342	Cortes
Ph I/II Randomized CA vs CI vs CIA	ID03-0181	Faderl
Ph I BAY-43-9006	2004-0702	Cortes
Ph I/II Alimta (Pemetrexed)	2004-0865	Kantarjian
Ph I SAHA + Idarubicin	2005-0031	Garcia-Manero
Ph I SNS-595	2005-0295	Kantarjian
Ph I/II MK-0457	2005-0330	Cortes
Ph I RTA 401 (CDDO)	2005-0469	Kantarjian
Ph I GX15-070MS	2005-0584	Borthakur
Ph I SJG-136	2005-0607	Ravandi
Ph I SAHA + DAC	2005-0723	Issa
Ph I Oral Sapacitabine	2005-0768	Kantarjian
Ph I/II CP-4055	2006-0132	O'Brien
Ph I/II AT9283	2006-0177	Kantarjian
Ph I FTS	2006-0201	Borthakur
Ph I Triciribine (TCN-PM, VD-0002)	2006-0249	Ravandi
Ph I KW-2449	2006-0275	Cortes

### CLL Treatment Priorities

#### 1. Untreated

- Fludarabine + Cytosan + Rituximab + GM-CSF (2006-0267)
- Rituximab + Sargramostin (2004-0102)
- CFAR (2005-0269)
- Kinetic Biomarker (2005-0528)
- Idiotype-KLH + GM-CSF (2005-1013)

#### 2. Prior Therapy

- Fludarabine + Cytosan + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- HuMax-CD20 (2006-0314)
- Clofarabine (2004-0134)
- Anti CD40 MoAb (2005-0025)
- Dasatinib (2005-0497)
- Forodesine HCL (2005-0290)
- 5-aza (2006-0428)
- CNF2024 (2005-0452)

#### 3. Other

- T-cell LPD: Alemtuzumab + Pentostatin (2004-0408)
- Hairy Cell: 2CDA + Rituximab (2004-0223)

### AML/MDS Treatment Priorities

#### 1. Newly Diagnosed

- Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Gemtuzumab (2006-0706)
- Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C + Gemtuzumab (2007-0147)
- Others: Ida + Ara -C (2006-0813)
  - IV Clofarabine (2005-0535/2006-0654)
  - Cloretazine (2006-0156)
  - Low Dose Decitabine +/- Valproic Acid (2006-0686)
  - DAC vs low-dose Ara-C (2005-0647)

#### 2. Salvage Programs

- Clofarabine ± Ida ± Ara-C (ID03-0181)
- Arsenic Trioxide + ATRA + Mylotarg (ID00-424) in APL
- Mitoxantrone + Etoposide + Ara-C CEP-701 (2003-0719)
- Cloretazine + Ara-C (2004-0639)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Ida + Ara-C + AEG (2005-0384)
- Oral Clofarabine (2005-0536)

(continued on page 7)

Cut out here

- 5-aza + Ara-C (2005-0291)
- CHIR-258 (2005-0674)
- MGCD0103 (2006-0474)
- AZD1152 (2006-0285)
- AC220 (2006-0850)

### 3. Low Risk MDS and CMML with <10% Blasts

- Cytokine Immunotherapy (2004-0253)
- Low dose Decitabine (ID03-0180)
- Oral SCIO-469 (2004-0790)
- Thymoglobulin + Cyclosporin (2005-0115)
- PR1 vaccine (2005-0913)
- AMG531 (2005-0577)
- Obatocalax Mesylate (2006-0688)

## ALL Treatment Priorities

### 1. Newly Diagnosed or Primary Refractory (one non-hyper-CVAD induction)

- A. Modified Hyper CVAD (ID02-230)
- B. Burkitt's: Hyper CVAD + Rituximab (ID02-229)
- C. PH+: Hyper CVAD + Dasatinib (2006-0478)
- D. Age <31: Augmented BFM (2006-0375)

### 2. Salvage Programs

- PH+: AMN107 (2004-0251)
- Augmented Hyper CVAD (ID03-0166)
- L-Annamycin (2004-0675)
- Forodesine HCL (2006-0595)
- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosan (2005-0552)
- 5-aza (2005-0895)

## CML Treatment Priorities

### 1. CML Chronic Phase

- BMS-354825 (2005-0422)
- AMN107 (2004-0251)
- Oral AMN107 (2005-0048)
- HHT + Gleevec (2005-0067)
- SKI-606 (2005-0813)
- MK-0457 (2006-0992)
- HHT (2006-0926)

### 2. CML Accelerated Phase

- AMN107 (2004-0251)
- HHT (2006-0926)
- SKI-606 (2005-0813)
- MK-0457 (2006-0992)
- HHT + Gleevec (2005-0067)

### 3. CML Blastic Phase

- GX15-07MS (2005-0584)
- AMN107 (2004-0251)
- ST157 + Idarubicin + Ara-C (ID01-300)
- HHT (2006-0192)
- MK-0457 (2006-0992)
- HHT + Gleevec (2005-0067)
- SKI-606 (2005-0813)

### 4. Minimal Residual Disease

- PR1 Vaccine + Gleevec (2006-0360)
- TALL-104 + Gleevec (2004-0837)
- Synthetic Vaccine (2005-0392)

### 5. Philadelphia-negative Myeloproliferative Disorders (MF, ET, PV, CEL/HES, Ph-neg CML)

- BMS-354825 (2004-0817)
- Lenalidomide + Prednisone (2005-0206)
- Pegasys (DM03-0109)
- Sunitinib (2006-0208)
- ST571 (ID01-167) (HES only)
- GX15-07MS (2006-0411)
- Velcade (2005-0284)
- 2CDA + Ara-C (DM97-232) (HES only)
- RAD001 (2006-0759)

## Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- Fenretinide (2005-0690)
- SAHA + DAC (2005-0723)
- SNS-595 (2005-0295)
- CP-4055 (2006-0132)
- MK-0457 (2005-0330)
- RTA 401 (CDDO) (2005-0469)
- AT9283 (2006-0177)
- FTS (2006-0201)
- SAHA+ Ida (2005-0031)
- Triciribine (2006-0249)
- GX15-07MS (2005-0584)
- KW-2449 (2006-0275)
- SJG-136 (2005-0607)
- INNO-406 (2006-0278)
- Sapacitabine (2005-0768)
- MGCD0103 + Aza (2005-0659)
- AVN-944 (2005-0609)

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