

Improving the Care of Patients with MDS

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Introduction

Over the last few years, the care of patients with MDS and the understanding of this disease have improved significantly. This has resulted in the development of new classifications of this heterogeneous group of leukemias as well as in the development of new therapies. New treatment strategies that are now considered standard of care include the hypomethylating agents (5-azacitidine and decitabine) and lenalidomide. MDS is one of the main areas of research of the Department of Leukemia at MD Anderson Cancer Center. This is demonstrated by the large number of clinical trials specific for patients with MDS (discussed below) and by extensive basic and translational research focusing on MDS as exemplified by the NIH funded MDS PO1 grant, now in its fourth year. Approximately, 300 patients with MDS are evaluated in our center per year by a group of physicians completely dedicated to the care of these patients. Most of this care is provided in close collaboration with the referring physicians, a key aspect for the long-term follow up of these patients most of which are older and require extensive care during therapy for their MDS.

In this Leukemia Insights issue, we describe part of the MDS program at MD Anderson with an emphasis on new therapeutic alternatives available at our center.

New prognostic classifications of MDS

One of the main problems in treating patients with MDS is the difficulty of its diagnosis and therefore classification. At MD Anderson, we have documented that in approximately 15% to 30% of patients referred to us there is a discrepancy with the outside diagnosis. In most instances, patients have acute myelogenous leukemia (AML) instead of MDS but patients with lower risk disease are also seen, as well as others with other conditions such as lymphomas, metastatic solid tumors and even no evidence of any pathological change at all. Therefore proper diagnosis is key when assessing these patients. Diagnosis of MDS requires a team of expert pathologists for the manual counting of blasts in the bone marrow, cytogenetics, and in some cases flow cytometry. Once the diagnosis is made, the question is what is the best approach: observation or initiation of therapy? Obviously this decision depends on the “risk” of the patient. Until recently most of the currently available classifications (FAB, WHO, or even the IPSS) were not accurate tools to predict the clinical behavior of patients with MDS, particularly those with lower risk disease. In the past at MD Anderson, many patients with MDS (those with blasts less than 10%) were referred back for “observation” only and therapy was recommended at the time of progression. We recently reviewed this practice in an analysis of the prognosis of patients with low or intermediate-1 risk disease by the IPSS referred to

(continued on page 2)

In This Issue

- 1 New Prognostic Classifications**
- 2 Treatment Options for Lower Risk Disease**
- 3 Treatment Options for Higher Risk Disease**
- 4 Treatment Priorities**

(continued from page 1)

our center over the last 25 years¹. We observed that most of these patients had a poor prognosis with a median survival in general less than 24 months (figure 1). Importantly, only 10% of these patients transformed to AML and it appears that most patients died from MDS related complications (i.e. infections, bleeding). This data indicates that “early intervention” in MDS may be beneficial and that specific therapeutic alternatives are needed for this group of patients that constitutes close to 70% of all patients with MDS.

Another important issue is the fact that technically, the IPSS score was applied at the time of initial diagnosis, a moment that is not always the time when therapeutic decisions are made. To overcome this problem, we have developed a new comprehensive classification² for all patients with MDS that we hope will become standard in MDS (Table 1). The other major advantage of this new system is that it does not require WHO assessment of the disease. A table to predict overall and 4-year survival is shown in table 2.

Table 1. MDACC Low risk MDS model

Adverse Factor	Coefficient	P value	Assigned Score
Unfavorable cytogenetics	0.203	<0.0001	1
Age ≥ 60 years	0.348	<0.0001	2
Hgb < 10 (g/dL)	0.216	<0.0001	1
Plt <50 x 109/L	0.498	0.0001	2
50-200 x 109/L	0.277		1
BM blasts ≥4%	0.195	0.0001	1

Therapeutic Alternatives at MD Anderson for Patients with MDS

Once the diagnosis of MDS is made and the patient is properly classified, the question is what is the best therapy for the patient. In our center, we still classify patients by IPSS score, although we may decide on introducing therapy earlier based on our new models described above. A list with characteristics of our current protocols is available at

Table 2. MDACC Low risk MDS model

Score	N	Median (months)	4-year survival (%)	Category
0	11	NR	78	1
1	58	83	82	1
2	113	51	51	1
3	185	36	40	2
4	223	22	27	2
5	166	14	9	3
6	86	16	7	3
7	13	9	NA	3

<http://www.mdanderson.org/diseases/mds>. The information provided in that website is continuously updated.

Treatment Options for Patients with Lower (Low and Intermediate-1 by IPSS) Risk Disease

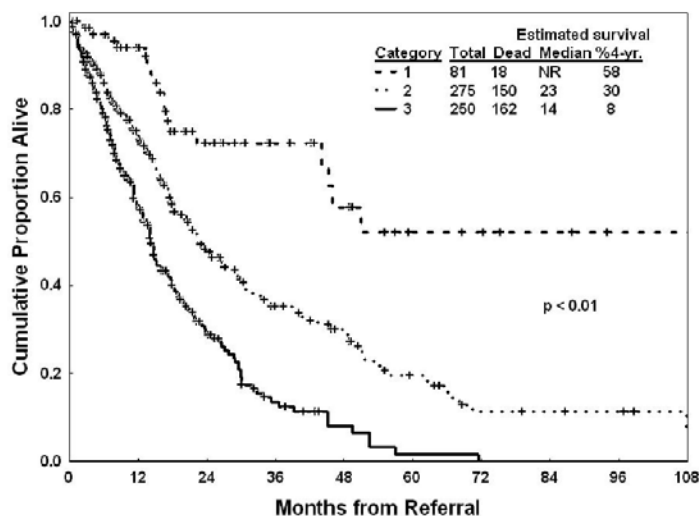
One key aspect of patients with low risk disease is to differentiate between those with so-called “hypocellular” MDS (a minority of patients) and those with hypercellular disease. This also serves to emphasize the need for bone marrow biopsies when initially evaluating patients with MDS to assess cellularity.

Current approaches include:

Protocol 2005-0115: Thymoglobulin and ATG. This study focuses on patients with hypoplastic MDS (bone marrow cellularity less than 20%). A response rate of 30% is being observed with an acceptable toxicity profile as we are using the rabbit ATG version.

Protocol 2007-0883: Low dose subcutaneous schedules of decitabine. Decitabine is one of the most active agents in higher risk MDS but current doses and schedules may be too intense for patients with lower risk MDS. We have developed a randomized phase II study of two schedules of SC decitabine, daily x 3 every month at a dose of 20

Figure 1. Survival of patients with lower risk MDS based on MDACC low risk model.



mg/m² versus weekly x 3 every 4 weeks at the same dose. This study is specific for patients with lower risk disease and may provide a safer more efficient dose/schedule of decitabine in this patient population.

Protocol 2007-04005: Oral 5-azacitidine.

5-azacitidine is very active in MDS and has been shown to improve survival in patients with higher risk disease. The main limitation is the need for several months to observe evidence of clinical benefit and the fact that currently treatment is considered indefinite. Because this agent is administered daily for 7 days either IV or subcutaneously, this becomes an issue when treating patients with MDS. Therefore the development of an oral formulation of this compound could have significant implications for our patients. We are part of a phase I study of an oral formulation of 5-azacitidine. Although the study is also open to patients with relapsed AML and MDS, patients with lower risk disease are also eligible. No significant toxicities have been encountered and clinical responses, including complete remission, are being observed. This study is a priority of the MDS program at MDACC.

Protocol 2006-0657: Combination of lenalidomide and darbopoeitin in patients without del5q alterations. Lenalidomide is an extremely active agent in patients with anemia and alterations of chromosome 5 (del5q). The activity of this drug in patients without del5q alteration is less significant.

Data from several investigators has indicated that the combination lenalidomide with growth factor may be synergistic. To study this issue, we have developed a study combining lenalidomide and darbopoeitin focusing on patients for whom anemia is the main problem.

Protocols 2006-0722 and 2008-0249: AMG-531 (Romiplostim). AMG-531 is a promising thrombopoiesis stimulating agent in MDS that has been recently approved for patients with ITP. The safety and response characteristics of this drug in MDS are not fully understood. At MDACC we have two studies using this drug. In the first one, AMG-531 is used in conjunction with decitabine. This is a very attractive combination that may reduce myelosuppression-related complications of decitabine. The second is a multicenter study of single agent AMG-531 for patients with MDS and thrombocytopenia that we expect will define the role of AMG-531 in lower risk MDS.

Upcoming studies in lower risk disease. Several studies are ready to be activated for patients with lower risk MDS. These concentrate on the development of several histone deacetylase (HDAC) inhibitors. Drugs like vorinostat³ have activity in AML. European investigators have reported clinical activity with weak HDAC inhibitors such as valproic acid in MDS⁴. Following this lead we are ready to open studies with LBH589, JNJ-26481585 and SBio939, three potent oral HDAC inhibitors. This class of drugs could become a new standard of care for patients with lower risk MDS.

Treatment Options for Patients with Higher (Intermediate-2 And High By IPSS) Risk Disease

Treatment of these patients still depends on age. Younger patients, particularly those with high risk disease are still considered for front-line induction chemotherapy approaches followed by allogeneic stem cell transplantation. For the older group of patients, which constitutes the majority, intensive chemotherapy is currently rarely indicated. Our strategies focus on development of active and safe treatments for newly diagnosed patients as well as those patients that have failed hypomethylating based therapies.

CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytosan + Rituximab (FCR) (2008-0431)
- FCR + Ofatumumab (2006-0839)
- Lenalidomide (2006-0715)

2. Prior Therapy

- Fludarabine + Cytosan + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- HuMax-CD20 (2006-0314)
- Dasatinib (2005-0497)
- OFAR2 (2006-1026)
- FCR ± Lumiliximab (2006-0789)
- 5-aza (2006-0428)
- Lenalidomide + Rituximab (2007-0208)
- SNS-032 (2006-0843)
- Alemtuzumab (2007-0626)
- ABT-263 (2007-0096)
- GS-9219 (2007-0087)
- Oral Clofarabine (2007-0905)
- 8-Chloro-adenosine (2004-0144)

3. Minimal Residual Disease

- Alemtuzumab vs Rituximab vs Both (2006-0767)
- Revlimid (2007-0213)

4. Other

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

AML/MDS Treatment Priorities

1. Newly Diagnosed

- A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Gemtuzumab (2006-0706)
- B. Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C + Gemtuzumab (2007-0147)
- C. Younger Patients:
 - IA + Sorafenib (2006-0977)
 - IA + SAHA (2007-0835)
- Older Patients:
 - Clofarabine + Ara-C + DAC (2007-0039)
 - Ida + Ara -C (2006-0813)
 - IV Clofarabine (2005-0535)
 - Low Dose Decitabine +/- Valproic Acid (2006-0686)

- DAC vs low-dose Ara-C (2005-0647)
- Obatoclax (2008-0037)
- SNS-595 (2007-0965)
- Vidaza ± MGCD0103 (2007-0763)
- Low dose Ara-C ± Lintuzumab (2008-0065)

2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Mitoxantrone + Etoposide + Ara-C + CEP-701 (2003-0719)
- Lenalidomide (2006-0293)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Oral Clofarabine (2005-0536)
- AZD1152 (2006-0285)
- AC220 (2006-0850)
- IA + Sorafenib (2006-0977)
- FAO (2006-1089)
- Azacitidine (2007-0405)
- DAC + Mylotarg (2007-0882)
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- CP-4055 (2006-0132)
- LY2181308 (2007-0707)
- Lenalidomide (2006-0293)

3. Maintenance Therapy

- DAC vs Observation (2006-0358)
- PR1 vaccine (2006-0904)

4. Low Risk MDS and CMML with <10% Blasts

- Decitabine (2007-0883)
- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- PR1 vaccine (2005-0913)
- AMG531 (2006-0772)
- Gimitecan (2006-0943)
- Romiplostim (2008-0249)
- Revlimid + Darbepoetin alfa (2006-0657)

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)
- E. T cell: Hyper CVAD + Nelarabine (2006-0328)

2. Salvage Programs

- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosan (2005-0552)
- 5-aza + Hyper CVAD (2005-0895)
- Marquibo (2006-1109)
- Augmented Hyper CVAD (ID03-0166)

CML Treatment Priorities

1. CML Chronic Phase

- Dasatinib (2005-0422)
- Bosutinib vs. Imatinib (2007-0709)
- Nilotinib (2005-0048)
- Bosutinib (2005-0813)
- Dasatinib (2007-0606)
- HHT (2006-0926/2006-0192)

2. CML Accelerated Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

3. CML Blastic Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

4. Minimal Residual Disease

- PR1 Vaccine + Gleevec (2006-0360)
- Dasatinib + Ipilimumab (2008-0157)

5. T315I Mutations

- XL228 (2007-0502)
- PHA-739358 (2007-0939)
- AP24534 (2008-0046)
- HHT (2006-0192)

Myeloproliferative Disorders

- Bevacizumab (2008-0025)(MF)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169/2008-0241)
- ST571 (ID01-167) (HES only)
- XL019 (2007-0373)(MF)
- 2CDA + Ara-C (DM97-232) (HES only)
- RAD001 (2006-0759)(SM)
- TG101348 (2007-0837)(MF)

Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- AT9283 (2006-0177)
- Triciribine (2006-0249)
- SJG-136 (2005-0607)
- INNO-406 (2006-0278)
- AZD4877 (2007-0287)
- XL228 (2007-0502)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)
- RO5045337 (2007-0408)
- OPB-31121 (2007-0488)
- ARRY-520 (2007-0879)
- SB1518 (2008-0032)
- AP24534 (2008-0046)

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(continued from page 3)

Protocols 2006-0977 and 2007-0835: Induction therapy approaches for younger patients with MDS. Traditional induction programs (i.e. “7+3” or IA) are relatively safe in patients younger than 60 years of age with induction mortality rates less than 10%. This type of approach followed by stem cell transplantation can be curative particularly in patients with diploid cytogenetics. Two phase II studies [IA+sorafenib (2006-0977) and IA+vorinostat (2007-0835)] are investigating the impact of adding a biological agent to standard induction approaches. So far, complete remission rates are extremely high with these programs and toxicities are not increased compared to the common experience with IA at MDACC. These biological agents are also used during consolidation and maintenance phases of the disease and may allow for long-term durable remissions in this difficult group of patients.

Protocols 2006-0686 and 2007-0882: Upfront therapy for older patients with MDS: combinations with decitabine. Data from our group has indicated that the combination of a hypomethylating agent and a histone deacetylase inhibitor has significant clinical activity and safety both in patients with higher risk disease and AML^{5,6}. One finding from these studies is that responses appeared to be higher and faster with the combinations and that patients with higher valproic acid levels in blood tended to have better response. To confirm the role of valproic acid in combination with decitabine, we are conducting an NIH funded phase II randomized study of decitabine with or without valproic acid (2006-0686). The results of this study will define the role of valproic acid in the treatment of patients with higher risk MDS in combination with decitabine. Another important study incorporates mylotarg with decitabine. Data from several groups has indicated that this combination may be very active in MDS/AML as well as safe as it utilizes a lower dose of mylotarg (3 mg/m² x 1). We are currently investigating the role of adding mylotarg to decitabine in study 2007-0882.

Therapy for patients that have received prior hypomethylating-based treatments. The use of 5-azacitidine and decitabine has been revolutionary for patients with higher risk disease. That said unfortunately most patients will eventually lose

response. Therefore new strategies are needed for this group of patients. It should be noted that there is no current FDA approved treatment approach for these patients except the use of allogeneic stem cell transplants or intensive induction therapies. We are developing a number of strategies for this very specific clinical situation.

Protocols 2005-0536 and 2005-0535: Clofarabine. Clofarabine is a nucleoside analogue with significant activity in patients with ALL and AML either as a single agent or in combination with cytarabine. In view of this, two studies are evaluating the safety and activity of lower dose schedules of both an IV and an oral formulation of clofarabine. Preliminary results from these trials were presented at the 2007 ASH meeting. Of importance, it was noted in this analysis that this intervention was very successful (around 40% response rate) in patients with MDS that had received prior hypomethylating agent based therapy.

Protocol 2006-0943: Gimatecan. DNA topoisomerase I inhibitors (such as topotecan) are known to have significant activity in MDS. Gimatecan is an oral topo I inhibitor. 2006-0943 is a phase I study evaluating the safety and activity of this compound in patients that have received prior therapy for MDS.

Protocol 2007-0727: Sapacitabine. Sapacitabine is a new oral nucleoside analogue being developed at MDACC with activity in AML and an excellent toxicity profile. Based on this, we are currently conducting a study of lower doses of sapacitabine for patients with higher risk MDS. An active oral approach in this setting would be of great interest.

Protocol 2006-0293: Lenalidomide in higher risk del5q MDS. The role of lenalidomide in higher risk MDS is not well defined. In this study we use lenalidomide for patients with higher risk disease or AML and an alteration of chromosome 5.

Allogeneic stem cell transplantation. The role of alloSCT in MDS is in evolution. Because most patients with MDS are older and may not have suitable related living donors, new transplant modalities are needed including those with lower intensity preparatory regimens. The Department of Leukemia collaborates closely with members of the Stem Cell Transplant Program at MD Anderson to evaluate patients for transplantation as soon as indicated.

In Summary

We believe that MDS will evolve as a major medical and societal problem as the US population ages and patients survive other malignancies. Thus the need for appropriate staging and risk stratification classifications and specific therapies for each subgroup of patients with MDS is clear. Ongoing research on the molecular basis of this disease will allow the development of new precise therapies for our patients. In our program we strive to complement our clinical experience with the latest concepts in the biology of this disease and believe in having therapeutic alternatives for all patients with MDS.

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