Leukemia INSIGHTS
VOL. 15 • NO. 2 SUMMER 2010

Advances in the Treatment of Myelodysplastic Syndromes

General Update

The myelodysplastic syndromes (MDS) include a very heterogeneous group of myeloid disorders characterized by ineffective hematopoiesis and transformation to acute myelogenous leukemia (AML). We find that a significant fraction of patients referred to the program come not only to discuss or receive advanced therapies but also for confirmation of their diagnosis. The main problem that physicians face when initially approaching a patient with MDS is the difficulty in establishing a morphological diagnosis. For instance, in approximately 30% of patients referred to our center, there is a discrepancy between the diagnosis at the time of referral and the final diagnosis. A referral to MD Anderson offers access to expert dedicated hematopathologists that focus exclusively on the diagnosis of leukemia and MDS. Furthermore, molecular diagnostic tools including conventional cytogenetics but also genetic analysis of alterations of genes such as Ras, Flt-3 and JAK2 (among several) are now part of the standard evaluation of a patient with MDS at MD Anderson. Once the diagnosis is established and confirmed, the next step is to predict the prognosis of an individual patient. Although tools such as the IPSS score are universally used, most investigators agree that these scores are not precise enough for patients with MDS, particularly for those patients in the lower risk categories. Other more recent models such as the WPSS score[1] require information, such as WHO diagnosis criteria or number of prior transfusions, which may not be readily available to many clinicians. Investigators at MD Anderson have developed new scoring systems for all categories of patients with MDS that allow for precise prediction of survival and transformation to AML.

Table 1 summarizes the Global MD Anderson MDS Score[2]. This model was recently validated by independent investigators at ASH 2009. Use of this model and the MD Anderson Lower-Risk Specific Model[3] enable decisions of when and in who to initiate therapy as well as how intense the therapy should be. The use of these tools thus allows for an individualized approach for patients with MDS.

In this Leukemia Insights, we summarize current therapeutic approaches to patients with MDS at our center.

If you have any questions about patients with MDS or any trial in particular, please do not hesitate to contact Dr. Guillermo Garcia-Manero at ggarciam@mdanderson.org or any of the Leukemia physicians for further information. A complete list of all trials currently available to patients with MDS at MDACC is available at http://www.mdanderson.org/

(continued on page 2)

In This Issue

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

TABLE 1 - Global MD Anderson MDS Score

Factors	Value / Ranges	Assigned Points
Performance Status (Zubrod)	0 or 1 ≥2	0 2
Age (years)	<60 60-64 ≥65	0 1 2
Platelets (K/uL)	<30 30-49 50-199 ≥200	3 2 1 0
Hemoglobin (G/DL)	<12.0 ≥12.0	2 0
Marrow Blast (%)	<5 5-10 11-29	0 1 2
White Blood Count (K/uL)	≤20 >20.0	0 2
Karyotype	-7, del(7)q or complex (≥3 abn) All Others	3 0
Prior Transfusion (RBC or PLT)	No Yes	0 1
Total	Low Int-1 Int-2 High	0-4 5-6 7-8 ≥9

patient-and-cancer-information/cancer-information/cancer-types/myelodysplastic-syndrome/index.html.

New Approaches to Patients With Lower Risk MDS

Patients with IPSS low or intermediate-1 disease are usually grouped together in the so-called lower risk category. These account for close to 75% of patients with MDS. This is a particularly difficult group of patients as it includes individuals with very benign conditions and long expected survivals and minimal risk of transformation to AML and patients with very poor prognosis and very high risk of transformation. The Lower-Risk Specific MDS model is used at MD Anderson to differentiate these patients (Table 2). One of the main emphases of our current therapeutic program is the development of new strategies specific for patients with lower-risk disease but poor predicted survival. Examples of several of these trials are summarized below.

Targeting the p38 MAPK pathway: A phase I trial of ARRY-614

p38 MAPK is involved in hematopoietic stem cell function. In vitro inhibitors of this pathway have been shown to stimulate hematopoiesis and have potential therapeutic benefit in patients with lower risk disease. ARRY-614 is a new oral molecule that inhibits p38 MAPK. This study is specific for patients with lower risk MDS that are transfusion dependent. So far toxicity has been minimal with this compound and hematologic responses are being observed in the initial phase of this trial. This is an option for transfusion dependent patients that are not responding to growth factor support.

TABLE 2 - MD Anderson Lower-Risk Specific Model

Factors	Value / Ranges	Assigned Points
Karyotype	Unfavorable	1
	Diploid or del(5)q only	0
Age (years)	<60	0
	≥60	2
Hemoglobin (G/DL)	<10.0	1
	≥10.0	0
Platelets (K/uL)	<50	2
	50-200	1
	>200	0
Marrow Blast (%)	<4	0
	≥4	1
Total	Low	0-2
	Intermediate	3-4
	High	≥5

Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors are a relatively new class of agents with activity in cutaneous lymphoma and potentially leukemia. In vitro, these agents have the capacity to induce cell differentiation and therefore there is significant interest in studying these agents in lower risk MDS. Because HDAC inhibitors are oral and have excellent toxicity profile, they are attractive for this group of patients. We are currently investigating two of these agents: LBH589 and JNJ-26481585.

LBH589 is a very potent oral hydroxamic acid derivative being explored in a number of leukemias and lymphomas. This phase II trial explores the activity of this agent in patients with low or int-1 disease that are transfusion dependent. The drug is administered three times a week and patients are not required to stay in Houston for a prolonged period of time.

JNJ-26481585 is a novel HDAC inhibitor that in vitro has an excellent antileukemia activity profile with minimal effect on normal hematopoietic tissues. We are currently conducting a phase I trial with extensive pharmacokinetic and dynamic monitoring to assess the safety and tolerability of this compound in both MDS (all risks) and AML.

New schedules of hypomethylating agents

Both 5-azacitidine and decitabine are approved for patients with MDS. That said current schedules of these agents, that are very effective in patients with higher-risk disease, are frequently associated with severe myelosuppresion. This may preclude their use in patients with lower-risk disease for whom this degree of myelosuppresion may not be acceptable. Because of the clinical activity of these agents, we have been interested in evaluating very low dose schedules of hypomethylating agents in patients with lower risk MDS. We just completed a study of decitabine comparing two different schedules: 20 mg/m^2 subcutaneous daily x 3 every month or the same dose weekly times three also every month. This study, which was presented at ASH 2009, demonstrated that the daily x 3 schedule was superior to the weekly. Although complete response rates were modest (less than 10%), close to 70% of patients achieved stabilization of disease and significant improvements in transfusion requirements. More importantly this very low dose schedule was extremely well tolerated with few complications from myelosuppresion. Based on these encouraging results, we are now designing a phase II trial of very low dose 5-azacitidine (50 mg/m^2 daily x 3) in transfusion dependent patients with lower risk disease.

This will serve as the basis for a planned study of oral 5-azacitidine that will be discussed below.

New Aproaches for Patients with Higher Risk Disease

The prognosis of patients with higher (IPSS intermediate-2 and high) risk MDS has improved significantly since the advent of the hypomethylating (HM) agents. Although the results with these two agents are encouraging, median survival of patients is still less than 24 months. More importantly the prognosis of patients that fail hypomethylating agents is very poor. Their median survival is less than 5 months and patients tend to be refractory to most conventional modalities. It is our opinion that most patients in this situation should be treated in a clinical trial when possible. The main objectives of the research program at MD Anderson for patients with MDS are twofold: development of new therapies that could improve outcomes in previously untreated patients and the development of therapies for patients that have failed a HM agent. The following are examples of these:

Combination epigenetic therapy

Results from several groups have demonstrated that the combination of a HM agent with an HDAC inhibitor is synergistic in vitro. Pilot phase II studies have also indicated that this type of approach is safe and active in patients with MDS and AML. To test this concept, we are currently conducting several studies of such combinations: a randomized clinical trial of single agent decitabine versus decitabine and valproic acid, the combination of 5-azacitidine and LBH589, and a study combining 5-azacitidine and vorinostat. This last study is open to patients who are not candidates for other regimens because they have impaired renal or hepatic functions, poor performance status, or have other active malignancies. Initial results of this trial are that this combination is safe and has activity in this group of patients that do not qualify in general for other therapeutic alternatives.

New hypomethylating agents: oral 5-azacitidine

An oral hypomethylating agent could provide significant benefit to patients with MDS. Not only would this be a more convenient approach to treatment but it would also allow the development of different schedules and potentially truly chronic use. At MD Anderson we have been developing an oral formulation of 5-azacitidine. Results of the initial phase I trial of oral 5-azacitidine were presented at ASH 2009. The drug was administered daily for 7 days following one cycle of standard subcutaneous 5-azacitidine to allow for intra-patient PK and PD analysis and the maximally tolerated dose (500 mg) was defined with the dose limiting toxicity being diarrhea. This GI toxicity is probably related to the fact that the formulation used contains a significant amount of mannitol. Response rates in patients that had received at least 7 cycles of therapy were in excess of 40%. Doses below the MTD (400 to 500 mg daily x 7) of oral 5-azacitidine have been very well tolerated. Based on extensive PK analysis, we are now investigating 15 to 30 day schedules as well as twice and three times a day administration. This study is open to patients with MDS, including previously untreated, and AML. Additional studies of other formulations of oral 5-azacitidine are ongoing at MDACC. A study with oral decitabine has also been recently opened at MDACC.

Other epigenetic combinations

The combination of 5-azacitidine and lenalidomide has recently been shown to be safe and active in MDS. Recent reports have also indicated that high dose lenalidomide (50 mg orally daily) has significant single agent activity in AML. Based on this, we are currently conducting a phase I trial of this combination using standard dose 5-azacitidine with dose escalation of lenalidomide in patients with MDS with or without deletion of chromosome 5q.

Another approach to enhance activity of HDAC inhibitors is via inhibition of the NF-kB pathway. Data from our collaborator Dr. Steven Grant at Virginia Comonwealth University has demonstrated that the combination of an HDAC inhibitor with bortezomib has significant activity in leukemia. We

are now currently conducting an NIH-funded trial of the combination of PDX1010, an oral HDAC inhibitor, and bortezomib in patients with MDS and AML. This study is specifically supported by the NCI and will allow us to understand the molecular and clinical implications of this type of combination therapy.

New agents in MDS: Patients for whom hypomethylating-based therapy is no longer effective

A number of non-hypomethylating nucleoside analogues are being developed for patients with MDS. These include clofarabine and sapacitabine. Both agents have significant activity in previously untreated patients and particularly in patients that have received prior HM therapy. Dr. Faderl reported data at ASH 2009 showing that oral clofarabine on a daily x 5 schedule had significant activity in patients with MDS including those who had received prior hypomethylating based therapy. Two other agents being studied in this group of patients are AR-67 and ARRY-520. AR-67 is a novel DNA topoisomerase I inhibitor, a class of agents that have demonstrated significant activity in the past in patients with MDS. ARRY-520 inhibits kinesin spindle protein or KSP and this approach has been shown to have antileukemia activity in preclinical models and to be safe in patients with advanced leukemia.

Specific situations and opportunities for patients with MDS

Access to multiple other trials in the Department of Leukemia offer the opportunity of other phase I trials for specific situations. Although Flt-3 and JAK2 mutations are relatively infrequent in MDS, patients with these features can be treated with specific targeted interventions. This includes the use of Flt-3 inhibitors and a number of JAK2 inhibitors. Also alternative higher dose schedules of lenalidomide are being explored in patients with alterations of chromosome 5.

Finally the group of patients with so-called hypoplastic MDS are currently being recognized as a different subset of patients that may not be candidates for standard therapies in MDS such as hypomethylating therapy or other forms of chemotherapy. Most investigators are focusing on immune manipulation in these patients using ATG combinations and more recently the use of alemtuzumab and these studies are also ongoing at MD Anderson.

The role of allogeneic stem cell transplantation and high dose chemotherapy in MDS

Although the median age of patients with MDS is 70 to 75 years, a significant fraction of patients are younger and may be potential candidates for more intense therapies including transplantation. The Leukemia Department works closely with the Department of Stem Cell Transplant at MD Anderson allowing for rapid evaluation and referral of such patients. Finally, even though the role of AML-like chemotherapy programs is debatable in MDS, it is obvious that younger patients can benefit from this type of approach, particularly those with diploid cytogenetics and a potential opportunity for transplantation. Current front line studies at MD Anderson include combinations using vorinostat, an HDAC inhibitor, or sorafenib, a Flt-3 inhibitor, or the incorporation of clofarabine to front line strategies. These studies may allow us to develop more effective induction/consolidation approaches both in MDS and AML.

References

1. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25:3503-3510.
2. Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer. 2008;113:1351-1361.
3. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia. 2008;22:538-543.

CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Lenalidomide + Rituximab (2008-0385)

2. Prior Therapy

- Fludarabine + Cytoxan + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- OFAR2 (2006-1026)
- 5-aza (2006-0428)
- FBR (2009-0546)
- ABT-263 (2007-0096)
- GS-9219 (2007-0087)
- 8-Chloro-adenosine (2004-0144)
- AMD 3100 (2008-0725)
- Milatuzumab (2008-0075)
- ABT-263 + FCR or BR (2009-0077)
- Lenalidomide + Ofatumumab (2009-0283)
- Revlimid (2007-0213)

3. Other

- 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)
- Ida + Ara -C (2006-0813)
- Clofarabine + IA (2009-0431)
- Plerixafor + Daunorubicin + Ara-C (2009-0503)

Older Patients:

- Low Dose Decitabine +/- Valproic Acid (2006-0686)
- Vorinostat + Aza (2007-0685)
- AZD1152 vs low-dose Ara-C (2009-0217)
- Vidaza + Revlimid (2009-0467)

2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Fludarabine + Ara-C +Mylotarg (2009-0781)
- Lenalidomide (2006-0293)
- Azacitidine (2007-0405)
- DAC + Mylotarg (2008-0288)
- Sapacitabine (2007-0727)
- LY2181308 (2007-0707)
- CPX-351 vs 'Standard' (2008-0679)
- DT388IL3 (2008-0313)
- PMA112509 (2009-0046)
- AZD1152 + Ara-C (2009-0172)
- Tosedostat (2009-0187)
- SAR103168 (2009-0196)
- Panobinostat (2009-0434)
- AEG35156 + IA (2009-0518)
- AC220 (2009-0560)
- PR104 (2009-0772)
- Alternating DAC + Sapacitabine (2009-1002)

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

- Oral Clofarabine (2005-0536/2007-0410)
- Lenalidomide (2006-0293)
- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- LBH589 (2007-0713)
- Romiplostim (2008-0249)
- JNJ-26481585 (2008-0245)
- AR-67 (2008-0530)
- ARRY-614 (2009-0129)
- Vorinostat + Aza (2007-0685)
- DAC +/- Clofarabine (2008-0092)
- Oral Decitabine (2009-0286)

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

- Clofarabine + Cytoxan (2005-0552)
- 5-aza + Hyper CVAD (2005-0895)
- MOAD (2008-0267)
- DT2219ARL (2008-0519)
- RAD001 + Hyper CVAD (2009-1000)

CML Treatment Priorities

1. CML Chronic Phase

- Dasatinib (2005-0422)
- Nilotinib (2005-0048/2009-0683)

2. CML Blastic Phase

- LY2181308 + IA (2007-0707)

3. T315I Mutations or Advanced Phases

- PHA-739358 (2007-0939)
- AP24534 (2008-0046)
- DCC-2036 (2008-0732)

Myeloproliferative Disorders

- Pomalidomide (2007-0199)(MF)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169)
- SB1518 (2008-0032)
- 2CDA + Ara-C (DM97-232) (HES only)
- AZD1480 (2009-0067)
- Masatinib (2008-0275)

Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- AT9283 (2006-0177)
- Bendamustine (2007-0634)
- SB939 (2007-0848)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)
- RO5045337 (2007-0408)
- OPB-31121 (2007-0488)
- AP24534 (2008-0046)
- JNJ - 26481585 (2008-0245)
- DCC-2036 (2008-0732)
- IPI-493 (2008-0786)
- IMC-EB10 (2009-0042)
- AS703026 (2009-0195)
- GSK1120212 (2009-0239)
- ABT348 (2009-0788)

List of Leukemia Service Attendings

ANDREEFF, MICHAEL	(713) 792-7260	KOLLER, CHARLES	(713) 792-7747
BORTHAKUR, GUTAM	(713) 563-1586	KONOPLEVA, MARINA	(713) 794-1628
BURGER, JAN	(713) 563-1487	KORNBLAU, STEVEN	(713) 794-1568
CORTES, JORGE	(713) 794-5783	MATTIUZZI, GLORIA N.	(713) 745-2723
ESTROV, ZEEV	(713) 794-1675	NGUYEN, KHANH	(713) 563-0295
FADERL, STEFAN	(713) 745-4613	O'BRIEN, SUSAN	(713) 792-7543
FERRAJOLI, ALESSANDRA	(713) 792-2063	QUINTAS-CARDAMA, ALFONSO	(713) 792-0077
FREIREICH, EMIL	(713) 792-2660	RAVANDI, FARHAD	(713) 745-0394
GARCIA-MANERO, GUILLERMO	(713) 745-3428	RYTTING, MICHAEL	(713) 792-4855
ISSA, JEAN-PIERRE	(713) 745-2260	THOMAS, DEBORAH	(713) 745-4616
JABBOUR, ELIAS	(713) 792-4764	VERMA, DUSHYANT	(713) 745-5789
KADIA, TAPAN	(713) 563-3534	VERSTOVSEK, SRDAN	(713) 745-3429
KANTARJIAN, HAGOP	(713) 792-7026	VU, KHANH	(713) 745-0655
KEATING, MICHAEL	(713) 745-2376	WIERDA, WILLIAM	(713) 745-0428

The University of Texas
M. D. Anderson Cancer Center
42860644
1515 Holcombe Blvd. - 428
Houston, Texas 77030-4009

Leukemia INSIGHTS

Funded in part by the Betty Foster Leukemia Fund

Leukemia Insights and other valuable information are now available via the World Wide Web.

Our address is: http://www.mdanderson.org/leukemia
or you may E-mail us at: ckoller@mdanderson.org

Editor: *Hagop Kantarjian, M.D.* WebMaster: *Charles A. Koller, M.D.*
Associate Editor: *Sherry Pierce, R.N.*

For referrals, please call 1-877-MDA-6789