Next Generation Approaches for Evaluation and Treatment of MDS

- Prognosis: IPSS-R
- Molecular characterization of MDS
- Impaired ribosome function & molecular basis of 5q- MDS
- Newer therapeutic agents/ approaches
- Stem cell transplantation
Updated prognostic assessment of MDS:
The Revised IPSS (IPSS-R)

Developed by the International Working Group for Prognosis in MDS (IWG-PM)

Peter Greenberg, MD
Stanford University Cancer Center
for the IWG-PM
MDS Classifications

- 1997 IPSS/IMRAW (FAB): 816 pts/7 DBs
  - Marrow blasts, cytogenetics, cytopenias
- 2001 WHO classification
  - Dysplastic subgroups, RAEB-1,2, del(5q)
- 2007 WPSS: 1165 pts/3 DBs
  - WHO subgroups, IPSS cytogenetics, RBC Txns
- 2001-2011 New features described as possible additional prognostic factors
- New cytogenetic classification: 2900 pts/4 DBs
- 2011 IWG-PM Refined consensus system (IPSS-R)
  - 7012 pts/18 DBs
IPSS-R Survival, n=7012

Fraction of patients

Months

very good
good
int
poor
very poor
Molecular Characterization of MDS Risk & Predisposition

Alan List, MD
H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL, USA
Regions of Likely aUPD in MDS

- SNP 6.0 analysis; n=148
- 63 tracts of copy neutral runs of homozygosity >20Mb in 46 (31%) cases
- 17 different chromosomes; 7 recurrent regions

Ernst et al., Nat Genet. 2010;42:722-6
Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Gailili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo García-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.

ABSTRACT

BACKGROUND
Myelodysplastic syndromes are clinically heterogeneous disorders characterized by clonal hematopoiesis, impaired differentiation, peripheral-blood cytopenias, and a risk of progression to acute myeloid leukemia. Somatic mutations may influence the clinical phenotype but are not included in current prognostic scoring systems.

C

--- Low risk, mutation absent (N=87)
--- Low risk, mutation present (N=23)
P<0.001
--- Intermediate-1 risk (N=185)

D

--- Intermediate-1 risk, mutation absent (N=128)
--- Intermediate-1 risk, mutation present (N=57)
P<0.001
--- Intermediate-2 risk (N=101)
Spliceosome abnormalities in MDS

A

SF3A1
U2snRNP
SF3B1
U1 snRNP
PRPF-40B
U2AF65
U2AF35
SR SRSF2
splicing enhancer
Exon 1
GU
UC
A
Exon 2
GU
AG
YRYRY

B

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Description</th>
<th>RARS/RCMD-RS</th>
<th>MDS without RS</th>
<th>CMML</th>
<th>t-MDS/sAML</th>
<th>Denovo AML</th>
<th>MPN</th>
<th>ALL</th>
<th>NHL</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF3B1</td>
<td>Predominant heterozygous missense mutations at K700, R625, and H662.</td>
<td>57 - 75.3%</td>
<td>6 - 20%</td>
<td>4.5 - 5%</td>
<td>4.8%</td>
<td>2.6 - 5%</td>
<td>3 - 4%</td>
<td>nd</td>
<td>nd</td>
<td>5%</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Recurrent heterozygous missense mutations at P95.</td>
<td>1.5%</td>
<td>11.6%</td>
<td>28.4%</td>
<td>6.5%</td>
<td>0.7%</td>
<td>1.9%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>U2AF35</td>
<td>Recurrent heterozygous missense mutations at S34 and Q157.</td>
<td>—</td>
<td>11.6%</td>
<td>8.0%</td>
<td>9.7%</td>
<td>1.3%</td>
<td>1.9%</td>
<td>—</td>
<td>—</td>
<td>nd</td>
</tr>
<tr>
<td>ZR51S2</td>
<td>Missense, nonsense and frameshift mutations throughout the open-reading-frame.</td>
<td>1.4%</td>
<td>7.7%</td>
<td>8.0%</td>
<td>1.6%</td>
<td>0.7%</td>
<td>1.9%</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>SF3A1</td>
<td>Missense mutations throughout the open-reading-frame.</td>
<td>—</td>
<td>1.3%</td>
<td>1.1%</td>
<td>1.6%</td>
<td>0.7%</td>
<td>—</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>PRPF40B</td>
<td>Missense mutations throughout the open-reading-frame.</td>
<td>—</td>
<td>1.9%</td>
<td>—</td>
<td>1.6%</td>
<td>0.7%</td>
<td>1.9%</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>U2AF65</td>
<td>Missense mutations throughout the open-reading-frame.</td>
<td>—</td>
<td>0.6%</td>
<td>1.1%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>SF1</td>
<td>Missense mutations in the proline-rich C-terminal domain.</td>
<td>—</td>
<td>1.3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.9%</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

O. Abdel-Wahab and R. Levine Cancer Cell 2011
Clinical Significance of SF3B1 Mutations

*Prolonged EFS independent of age, gender and karyotype.

Familial MDS
Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia

Christopher N Hahn¹,², Chan-Eng Chong¹,²,¹⁴, Catherine L Carmichael³,¹⁴, Ella J Wilkins³,¹³, Peter J Brautigan¹, Xiao-Chun Li¹, Milena Babic¹, Ming Lin¹, Amandine Carmagnac³, Young K Lee¹, Chung H Kok⁴,⁵, Lucia Gagliardi¹, Kathryn L Friend⁶, Paul G Ekert⁷, Carolyn M Butcher⁴,⁵, Anna L Brown⁵, Ian D Lewis²,⁵, I Bik To²,⁵, Andrew E Timms⁸, Jan Storek⁹, Sarah Moore¹, Meryl Altree¹⁰, Robert Escher³,¹³, Peter G Bardy⁵, Graeme K Suthers¹⁰,¹¹, Richard J D’Andrea²,⁴,⁵,¹⁵, Marshall S Horwitz⁸ & Hamish S Scott¹–³,¹²,¹⁵
Ribosome function and the molecular biology of the 5q-syndrome

Jackie Boulwood

LLR Molecular Haematology Unit
John Radcliffe Hospital
Oxford
A p53-dependent mechanism underlies macrocytic anemia in a mouse model of human 5q− syndrome

Jillian L Barlow¹, Lesley F Drynan¹,⁴, Duncan R Hewett¹,⁴, Luke R Holmes¹,⁴, Silvia Lorenzo-Abalde¹

Identification of miR-145 and miR-146a as mediators of the 5q− syndrome phenotype

Daniel T Starczynowski¹,², Florian Kuchenbauer¹, Bob Argiropoulos¹, Sandy Sung¹, Ryan Morin¹, Andrew Muranyi¹, Martin Hirst¹, Donna Hogge¹, Marco Marra¹, Richard A Wells³, Rena Buckstein³, Wan Lam¹,², R Keith Humphries¹,⁴ & Aly Karsan¹,²
Combinational therapy and newer agents in MDS- my perspective

Prof Ghulam J. Mufti
MDS foundation
ASH 2011
NOVEL Nucleoside analogues

SAPACITABINE

CLOFARABINE

Is there a role for GO?


Tosedostat-Aminopeptidase inhibitor

Lowenberg B, JCO 2010.
Advances in HSCT for MDS: Cord Blood Transplantation & RIC

Juliet N. Barker, MBBS (Hons), FRACP
Associate Attending
Director Cord Blood Transplant Program
Memorial Sloan-Kettering Cancer Center
MSK Double Unit CBT: Engraftment & Survival
N = 54, median 42 yrs (range 7-66), high risk heme malignancies

One unit wins. High rates of sustained neutrophil engraftment despite low cell dose of engrafting unit.

Promising survival.

Barker et al, BBMT 2009
About the Foundation

Who Are We?
The Myelodysplastic Syndromes Foundation, Inc., was established in 1994 by an international group of physicians and researchers to provide education about MDS to physicians and patients, support for MDS research, patient support, and advocacy.

JOIN US AS AN MDS CENTER OF EXCELLENCE

Apply for The Centers of Excellence Program:
Would you like your treatment center to become part of the Foundation’s research network and referral system for MDS patients?
Please call us for more information and an application.

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The 12th International Symposium on 
MYELODYSPLASTIC SYNDROMES

May 8-11, 2013  |  Berlin, Germany

ADVANCING RESEARCH & PATIENT CARE

Save the Date

Symposium Chairmen:
Arnold Ganser, M.D., Ph.D.
Hannover Medical School, Germany
Wolf-Karsten Hofmann, M.D., Ph.D.
University Hospital Mannheim, Germany

www.kenes.com/mds