Impact of Comorbidity on Quality of Life and Clinical Outcomes in MDS

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Disclosures:

Honoraria: Celgene
Pathogenesis of MDS

- Clonal Hematopoiesis
- Stem Cell-Derived (Permanent) Clones
- Dysplasia and Apoptosis
- Step-wise Process $\rightarrow$ secondary AML
- Role of the Microenvironment
- Treatment-Related Factors (e.g. Iron)
- Role of Age and Organ-Function
- Role of Co-Morbidities
- Role of other Patient-related Factors
Pathogenesis of MDS

Clonal expansion of a premalignant progenitor cell population leading to ineffective (impaired) erythropoiesis / hematopoiesis

Disease manifestation may depend on EPO production (kidney function↓? androgens↓?)

EPO production adequate and sufficient to prevent anemia

Inadequate ‘EPO-response’ to ineffective erythropoiesis → anemia

Low EPO in elderly → anemia / AOE

EPO-responsive progenitors

no MDS detected as no anemia develops – these patients have dysplasia without cytopenia = IDUS

Low EPO overt MDS

HIGH RISK MDS (cytopenia found invariably)

Further oncogenic hits that lead to maturation arrest and proliferation

SECONDARY ACUTE MYELOID LEUKEMIA

EPO as co-factor

IDUS+ICUS=MDS

Valent et al., Leuk Res 2007;31:727
Valent, Leuk Res 2008;32:1333

Normal Hematopoiesis

in the elderly

Normal Hematopoiesis in the elderly

Low EPO in elderly

ICUS-A

Valent, Leuk Res 2008;32:1333

Low EPO overt MDS

LOW RISK MDS often responsive to EPO therapy (15-25% of patients)

Disease progression/clonal expansion

EPO-responsive progenitors

EPO-response lost +/- blasts ↑

EPO-responsive progenitors
WHO 2008 Classification of MDS*

(www.who.int/bookorders/)

- Refractory Cytopenias with Unilineage Dysplasia (RCUD)
  - Refractory Anemia (RA)
  - Refractory Neutropenia (RN)
  - Refractory Thrombocytopenia (RT)
- Refractory Anemia with Ring Sideroblasts (RARS) (≥15%)
- Refractory Cytopenia with Multilineage Dysplasia (RCMD)
- Refractory Anemia with Excess Blasts-1 (RAEB-1) (<10%)
- Refractory Anemia with Excess Blasts-2 (RAEB-2) (≥10%)
- Myelodysplastic Syndrome - Unclassified (MDS-U)
- MDS associated with isolated del(5q) [the only cytogenetic variant]
- [Childhood Myelodysplastic Syndrome (separate subchapter, separate authors)]

*WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, 2008, Chapter 5, Pages 88-107
Classification of MDS According to Etiology

1) Primary \textit{(de novo)} MDS
   - No Mutagenic Event in CH
   - No Previous CT or SCT
   - No Previous Radiation

2) Secondary MDS
   - Mutagenic Event known
   - Even if many Years ago
   - Often with Complex Biology
   - Often with Complex Karyotype
Classification of MDS According to Age

1) Childhood MDS (also by WHO)
2) MDS in Younger Adults
   - Often Fit and Transplantable
   - Few or no Comorbidities
   - EPO Production usually normal
3) MDS in The Elderly ($\approx > 70$ yrs)
   - Often “Not So Fit“
   - Comorbidities often present
   - EPO Production often impaired
   - Often Complex Disease Biology
Treatment Algorithms in Patients with MDS

Risk stratification of patients with acute myeloid leukemia or MDS receiving allogeneic HCT

Sorror et al. JCO 2007;25:4246-4254

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NRM, nonrelapse mortality
OS, overall survival
RFS, relapse-free survival.

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Age and Comorbidity

HCT-CI score 0, white area;
HCT-CI scores 1 to 2, gray area;
HCT-CI scores more than or equal to 3, black area.

Sorrer et al., Blood 2007;110:4606-4613
OS and event-free survival (EFS) according to HCT-CI groups

All MDS Patients

IPSS Low + Int-1 MDS Patients

Impact of Comorbidities (ACE-27) on Survival in Patients with MDS

Adult Comorbidity Evaluation-27 (ACE-27) comorbidity score

Naqvi et al, J Clin Oncol 2011;29:2240-2246.
Three different End Points in MDS: Survival, AML-Evolution, QOL

**Disease-related Factors:**
- Karyotype and Molecular Lesions
- Blast Cell Count, Blood Counts
- Histologic BM Patterns e.g. Fibrosis
- Flow Patterns, EMI, Splenomegaly

**Patient-related Factors:**
- Age, Mutagenic Events, ECOG
- Gender, Germline Patterns, SNP
- Social Factors, Psychology
- CoMorbidities

**MDS**

- Management Therapy
- Natural Course
- Overall Status
  - Mental Strength

**Overall Outcome**

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International Prognostic Scoring System (IPSS) - Classification

Freedom from AML evolution

Survival

Patients (%)

Time (years)

Patients (%)

Time (years)

Low  Int-1  Int-2  High

Greenberg et al. Blood. 1997;89:2079

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The revised IPSS = IPSS-R
Survival and AML-free Survival

Survival Probability

AML-Evolution Probability

Greenberg et al, Blood 2012;120:2454-2465
WHO-based Prognostic Scoring System = The WPSS: Cumulative Survival

The Problem in MDS: What Therapy in what Patients?

The available Scoring Systems are still not always optimal!

Not optimized for Endpoints

We need better Score-Models that include recommendations:

GO-GO, SLOW-GO, NO-GO!
## Impact of Comorbidities (ACE-27) on Survival in Patients with MDS

### Multivariate Survival Model and Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.582</td>
<td>2</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ACE-27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>0.301</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>0.782</td>
<td>3</td>
</tr>
<tr>
<td><strong>IPSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INT-2</td>
<td>0.512</td>
<td>2</td>
</tr>
<tr>
<td>HIGH</td>
<td>0.769</td>
<td>3</td>
</tr>
</tbody>
</table>

*Score points were obtained by dividing estimated coefficients by 0.3.

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![Survival Graph](image)

### Survival (95% CI)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Total</th>
<th>Dead</th>
<th>Median (mos)</th>
<th>5-yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>116</td>
<td>61</td>
<td>43 (36 to 65)</td>
<td>43 (34 to 55)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>288</td>
<td>212</td>
<td>23 (19 to 27)</td>
<td>22 (17 to 27)</td>
</tr>
<tr>
<td>High</td>
<td>191</td>
<td>179</td>
<td>9 (7 to 11)</td>
<td>5 (3 to 10)</td>
</tr>
</tbody>
</table>

Naqvi et al, J Clin Oncol 2011;29:2240-2246.
The MDS-specific comorbidity index (MDS-CI) Italian – German Collaboration

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>HR obtained through a multivariable Cox’s survival analysis with NLD as an outcome</th>
<th>Variable weighted score (to be taken into account if the specific comorbidity is present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disease</td>
<td>3.57 ($P&lt;0.001$)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate-to-severe hepatic disease</td>
<td>2.55 ($P=0.01$)</td>
<td>1</td>
</tr>
<tr>
<td>Severe pulmonary disease</td>
<td>2.44 ($P=0.005$)</td>
<td>1</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.97 ($P=0.04$)</td>
<td>1</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2.61 ($P&lt;0.001$)</td>
<td>1</td>
</tr>
</tbody>
</table>

MDS-CI in various WPSS groups (OS)

![Graphs showing survival analysis for different WPSS groups](image)

- **WPSS Very Low + Low**
- **WPSS Int**
- **WPSS High**
- **WPSS Very High**

**Della Porta et al, Haematologica 2011;96:441-449**
New Score for Optimal Prediction of Survival in Patients with MDS

Score:
1) IPSS points
2) Ferritin <900 = 0
   ≥900 = 1
3) Age < 70 = 0
   70-79 = 0.5
   ≥80 = 1.5
4) HCT-CI
   Low/Med = 0
   High = 0.5

LOWs = 0           INT-1s = 0.5-1.0
INT-2s = 1.5-2.0   HIGHs = >2

Therapy Options in MDS

Wait and Watch

Best Supportive Treatment
(Tf, EPO sc, AB, ..)

Non-Intensive Antineoplastic Therapy &
Less Intensive Therapy (Azacytidine)

Intensive Antineoplastic Drug Therapy

Stem Cell Transplantation

Experimental Treatment
PROPOSED STRATIFICATION MODEL

1) Estimate Survival Compared to the Natural Survival in Age-Matched Healthy Controls
   = Score A optimized for Survival Prediction

2) Estimate Risk of AML Development (largely independent of Patient-Related Factors)
   = Score B optimized for AML Prediction

3) Determine Therapy-Options based on Patient-Related Factors (Age, ECOG, etc), MDS type and Score A plus Score B combined assessment

4) Final Proposal: NO-GO, SLOW-GO, GO-GO
PROPOSED MODEL: EXAMPLES

Example #1
Age 59, ECOG = 0, Score A Low & Score B High
= GO GO (CT + SCT)

Example #2
Age 67, ECOG = 2, Score A High & Score B Low
= NO GO (best supportive care)

Example #3
Age 70, ECOG = 1, Score A Int & Score B High
= SLOW GO (for example azacytidine)
Dynamic Scoring and Risk Assessment in the Follow-Up (FU) in Patients with MDS

- Dynamic Scores and Variables:
  - WPSS, other novel Scores
  - LDH in the FU as robust prognostic Variable
  - Cytopenias and Karyotype (IPSS Variables)

- Age increases in the FU!
- Comorbidities may worsen
- Some Comorbidities may improve or even resolve
- Physicians follow and address Comorbidities
General Approach to MDS Patients suffering from Co-Morbidities

- **Risk Assessment and Prognostication:**
  a) Survival  
b) AML Evolution

- **Optimal Management of Co-existing Disorders**

- **Elimination of all Risk Factors** (e.g. Iron Overload)

- **Age- and Comorbidity-Adjusted Support:**
  a) Hemoglobin >8 g/dL; >10 g/dL (O₂ demand)  
b) Platelets depending on Comorbidities  
c) Antibiotics and G-CSF (consider Comorbidities)

- **Overall Treatment Plan Adjusted to Age and various Comorbidities** (cardiac and others)
Clinical Impact of Iron Overload and Iron Chelation in MDS

• Natural Course: Survival, AML Development?
• SCT: Pre-Transplant Ferritin Levels → Prognosis
• Comorbidity: DM, Cardiac Function (CT/SCT possible?)
• Comorbidity → Quality of Life (QOL)

• Sufficient Iron Chelation can be achieved in MDS
• New Chelating Agents; these are oral Drugs (QOL)
• Important Question may be: Life Expectancy → needs a Score System optimized for predicting survival: IPSS, Age, Comorbidity, Ferritin
Previous Guidelines

- **Italian Society for Hematology Guidelines (2002)**
  - indication: > 50 red cell units (RCU) + > 6 months LE
  - deferoxamine s.c.

- **United Kingdom (U.K.) MDS guidelines (2003)**
  - indication: > 5 g iron (>25 RCU) + long term transfusion pts
  - deferoxamine s.c.

- **Nagasaki Consensus Meeting guidelines (2005)**
  - indication: stable disease, ferritin > 1,000 > 2,000 µg/L, pre-SCT pts

  - indication: > 20-30 RCU + ongoing transfusions, ferritin > 2,500 µg/L co-morbidity (additional risk factors for organopathy)
  - deferoxamine s.c. or deferasirox p.o.

- **Florence Consensus Meeting guidelines (2007/2008)**
  - indication: ferritin > 1,000 and/or 2 RCU per months for > 1 year, LE > 1 year, ferritin as follow up parameter (every 3 months), pre-SCT
  - deferoxamine s.c. or deferasirox p.o. or deferiprone p.o. (no response to other therapies)

Gattermann, Leuk Res 2007;31(S3):10-15
How to measure QOL?

- ´Semi-Objective´ Parameters: ECOG …
- Questionnaire-based evaluation …
- Validated QLQ Scores: EORTC QLQ-C30
- Only a few standardized and validated forms and approaches are available
- QOL may change over time and depends on many factors and overall situation in each case
- QOL may also change with social, private, economic and other factors/conditions
QOL in MDS: Pre-treatment Symptom Prevalence assessed by QLQ

EORTC QLQ-C30

Fatigue is a Relevant and Frequent Symptom in MDS and impairs QOL

Efficace et al, Br J Haematol 2014, in press
QOL is always relative & subjective

• QOL may change over time and depends on many factors and the overall situation in each case

• QOL may also change with social, private, economic and other factors/conditions

• QOL may depend on the living place and on technical or environmental factors

CAN WE ALWAYS MEASURE QOL:

- IN A CLINICALLY RELEVANT WAY?

- IN A PATIENT-RELEVANT MANNER?
QOL is always relative & subjective
Myelodysplastic Syndromes

THANK YOU FOR YOUR ATTENTION!

Peter Valent & MDS Study Group Vienna & MDS Platform of the Austrian Society for Hematology and Oncology

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Treatment Algorithms in Patients with MDS

MDS

very young -> young -> middle aged -> old -> very old

stem cell transplantation

induction chemotherapy

dose-reduced, targeted or exp. drugs

consolidation chemotherapy

treatment failure, relapse

long term survival

consider: WHO or FAB-group, IPSS, performance status, dynamics of progression, duration of disease, de novo vs secondary, targets, co-morbidity!
HIERARCHY AND SUBCLONE FORMATION FROM NEOPLASTIC STEM CELLS DURING EVOLUTION OF CANCER AND LEUKEMIA*

*Many Observations were made in the Paradigmatic CML Model, based on Evolution of Subclones carrying BCR/ABL Mutations

- Long Latency Periods (Decades) in early Phases of LSC Evolution
- Premalignant Neoplastic Stem Cells versus Malignant SC = CSC/LSC
- Extensive Subclone Formation
- Each Subclone contains its own Stem Cell Compartment
- Phenotypic, Biochemical and Functional Heterogeneity
- Different Mechanisms of Drug Resistance in Subclones

Premalignant Neoplastic Stem Cells
Malignant Neoplastic Stem Cells
= Cancer Stem Cells = LSC

Overt Cancer
Hierarchical and Subclone Formation from Neoplastic Stem Cells During Evolution of Cancer and Leukemia

- Long Latency Periods (Decades) in early Phases of LSC Evolution
- Premalignant Neoplastic Stem Cells versus Malignant SC = CSC/LSC
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MDS: Minimal Diagnostic Criteria

A. Prerequisite Criteria (BOTH MUST be fulfilled)
- Constant Cytopenia (one or more lines, 6 mo unless abnormal karyotype present)
- Exclusion of all other hematopoietic and non-hematopoietic diseases as primary reason for cytopenia/dysplasia (co-existing neoplasm or AML: needs BM histology)

B. MDS-related (decisive) Criteria (at least ONE)
- Dysplasia in at least 10% of: erythrocytes or/and megakaryoc. or/and neutrophils or/and >15% ring sideroblasts (iron stain)
- 5-19% blast cells in bm smears
- Typical karyotype abnormality (conventional cytogenetics or FISH)

C. Co-Criteria* (pts fulfilling A but not B & typical clinical features)
- Abnormal phenotype of bm cells by flow cytometry
- Molecular features indicative of a monoclonal disease process
- Constantly reduced bm function (e.g. low CFU levels)

*In the absence of B, Co-Criteria may lead to the prefinal diagnosis: highly suspective of MDS

Valent et al., Leuk Res 2007;31:727
MDS: Minimal Diagnostic Criteria

What if a Patient does not fulfil minimal diagnostic criteria for MDS?

1) **ICUS**: Idiopathic Cytopenia of US

2) **IDUS**: Idiopathic Dysplasia of US

Valent et al., Leuk Res 2007;31:727

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Definition of ICUS = 
Idiopathic Cytopenia of Uncertain (Undetermined) Significance

- Constant (≥ 6 m) marked cytopenia (Hb<11; ANC<1000; PLT<100000)

- MDS excluded! - no decisive criterion / B!

- All other causes of cytopenia also excluded*

*Studies include a BM investigation (smear + histology), chromosome analysis (± FISH), various lab parameters, etc!

Valent et al., Leuk Res 2007;31:727
Definition of IDUS =
Idiopathic Dysplasia of Uncertain (Undetermined) Significance

- No constant ($\geq 6$ m) marked cytopenia
- MDS-like features: dysplasia $\pm$ karyotype!
- All other causes of dysplasia excluded*

*Studies include a BM investigation (smear + histology), chromosome analysis ($\pm$ FISH), and various lab parameters

Valent et al., Leuk Res 2007;31:727
Low EPO in the elderly & ICUS / IDUS

EPO as co-factor in MDS

Clonal expansion of a premalignant progenitor cell population leading to ineffective (impaired) erythropoiesis / hematopoiesis

First hits - mutagenic event/s?

Disease manifestation may depend on EPO production (kidney function↓? androgens↓?)

EPO production adequate and sufficient to prevent anemia

Inadequate ‘EPO-response’ to ineffective erythropoiesis → anemia

no MDS detected as no anemia develops – these patients have dysplasia without cytopenia = IDUS

LOW RISK MDS often responsive to EPO therapy (15-25% of patients)

Disease progression/clonal expansion

HIGH RISK MDS (cytopenia found invariably)

Further oncogenic hits that lead to maturation arrest and proliferation

SECONDARY ACUTE MYELOID LEUKEMIA

Normal Hematopoietic Stem Cell

Normal Hematopoiesis in the elderly

Low EPO in elderly → anemia / AOE

ICUS
**IDUS + ICUS = MDS**

- MDS may often develop early in lifetime – usually as a clinically silent prephase = IDUS (if detected)
- In young patients with IDUS and EPO-responsive BFU-E, the EPO production may be sufficient to prevent the development of anemia
- **With age, EPO production decreases and these patients develop anemia and thus frank MDS**
- Reason for decreased EPO production in advanced age: **a) renal = ‘aged kidney’ [b) androgen deficiency]** studies are in progress to answer this question!
- **IDUS must not be confused with imminent AML!** How to differentiate: 1) CFU 2) 6 months!