La anemia en los síndromes mielodisplásicos (SMD)

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I CONGRESO NACIONAL DE ANEMIAS RARAS Y SÍNDROMES RELACIONADOS

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Contents of the talk

- Introduction
- Importance of anemia
- Prognostic stratification
- Treatment of anemia
  - Lower-risk patients
  - Higher-risk patients
Myelodysplastic syndromes

- Heterogeneous group of clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis, leading to cytopenia(s) in the presence of hypercellular bone marrow and morphological dysplasia, and high propensity to evolve to AML
- 3 – 5 cases per 100,000 population per year
- Affects primarily elderly people (median age, 75 yr)
- Clinical course very variable (few weeks to many years)
- HSC transplantation only proven curative treatment alternative
WHO classification 2008

- Refractory cytopenia with unilineage dysplasia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia +/- ring sideroblasts
- Refractory anemia with excess blasts (RAEB-1, 5-9%; RAEB-2, ≥10%)
- MDS-unclassified
- MDS with isolated del(5q)

*Cazzola et al., Hematol Clin Oncol North Am 2010*
Clonal diversity of recurrently mutated genes in MDS

Targeted seq 94 genes in 157 MDS or sAML

Distinct differences between MDS and AML

Importance of anemia in MDS

• High incidence at diagnosis, greater during evolution
  – Anemia symptoms at diagnosis: 50% - 70% of patients
  – Hb < 10 g/dL at diagnosis: 50% - 80% of patients

• Clinical relevance
  – Cardiac remodeling and increased incidence of heart failure
  – Iron overload due to chronic RBC transfusions
  – Poorer quality of life
  – Shorter survival

• Most frequent cause for starting treatment in lower-risk patients

Effect of anemia on survival in MDS

Transfusion dependence decreases survival rates

Overall survival¹
(N = 467; HR = 1.91; p < 0.001)

Overall survival²
(HR = 1.36; p < 0.001)

HR = hazard ratio; pRBC = packed red blood cells.

Survival and AML risk by WPSS

Overall survival
(P<.001)

Risk of AML evolution
(P<.001)

Risk of non-leukemic death by degree of anemia in MDS and gender

Males

Females

Risk of developing cardiac disease and death by degree of anemia in MDS

Impact on survival and AML risk of RBC transfusion dependency in MDS patients (US Medicare)

RBC transfusion-dependent patients had a higher prevalence of different complications

Impact on survival and AML risk of RBC transfusion dependency in MDS patients (US Medicare)

RBC transfusion-dependent patients experienced shorter OS and higher risk of AML

Overall survival of RBC transfusion-dependent and non-transfusion-dependent patients (European LeukemiaNet)

Significantly greater mortality was noted in RBC transfusion-dependent patients.

Adapted from de Swart L, et al. Blood. 2011;118:[abstract 2775].
High serum ferritin is associated with worse overall and AML-free survival in MDS

Quality of life is associated with hemoglobin level in cancer patients

Anemia and quality of life in MDS patients
(Nordic MDS study Group)

- Darbepoetin ± G-CSF to achieve a hemoglobin target of 12 g/dL at week 16. Complete responders continue treatment until week 26. Non-responders received RBC transfusions to achieve that target.
- Quality of life (QOL) was assessed at week 26.

DBP complete responders (n = 10)

Transfused patients (n = 19)

Nilsson-Ehle H et al. *Eur J Haematol.* 2011;87:244-52
Treatment of MDS: General principle

- Great prognostic heterogeneity
- Advanced age
- Comorbidity and associated diseases frequent
- Curative modalities (i.e. allo-HSCT): high morbidity and mortality

Risk-adapted treatment essential
**IPSS-R: Prognostic score values**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category, points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
</tr>
<tr>
<td>Very Good</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
</tr>
<tr>
<td>Very Poor</td>
<td>4</td>
</tr>
<tr>
<td>BM blast, %</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2 and &lt;5</td>
<td>1</td>
</tr>
<tr>
<td>5 - 10</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3</td>
</tr>
<tr>
<td><strong>Hb, g/dL</strong></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>0</td>
</tr>
<tr>
<td>8 - &lt;10</td>
<td>1</td>
</tr>
<tr>
<td>&lt;8</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>ANC, x 10^9/L</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;0.8</td>
<td>0</td>
</tr>
<tr>
<td>≤0.8</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Platelets, x 10^9/L</strong></td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>0</td>
</tr>
<tr>
<td>50 - &lt;100</td>
<td>0.5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>1</td>
</tr>
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## IPSS-R: Risk groups and scores

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score (points)</th>
</tr>
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<tbody>
<tr>
<td>Very low</td>
<td>0 – 1.5</td>
</tr>
<tr>
<td>Low</td>
<td>2 – 3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5 – 4.5</td>
</tr>
<tr>
<td>High</td>
<td>5 – 6</td>
</tr>
<tr>
<td>Very-high</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

Risk-adapted treatment of MDS

Prognostic scoring systems: IPSS-R

Survival

AML-free survival

- Improved predictive power and validated in external series but more complex

Treatment approaches are limited

Two risk groups recognized in daily practice

- Lower-risk
- Higher-risk
Risk-adapted treatment of MDS
GESMD definition of higher risk patients

- IPSS-R high or very high
- IPSS int-1 with one or more of the following features
  - High or very high risk cytogenetics (by IPSS-R)
  - Severe neutropenia (< 0.5 × 10^9 PMN/L)
  - Severe thrombocytopenia (< 30 × 10^9 platelets/L)
  - Moderate/severe BM fibrosis (grade 2 – 3)

**Advantage:** Symptomatic anemia only reason for treatment remaining in patients with lower-risk MDS

Treatment modalities for MDS
Goals of treatment and candidates for active treatment

- Lower-risk patients
  - **Goal**: Improve symptoms and quality of life
  - **Candidates**: Symptomatic cytopenia/s (anemia) present. A watchful waiting strategy requires careful monitoring

- Higher-risk patients
  - **Goal**: Modify natural history of the disease and improve survival
  - **Candidates**: All patients. Avoid delay
Treatment modalities for MDS

Best supportive care

- Best supportive care (BSC) remains essential for the appropriate management of every single patient with MDS.

- BSC includes:
  - RBC transfusions
  - Platelet transfusions
  - Antimicrobial therapy
  - Iron chelation
**Therapeutic algorithm for lower-risk MDS patients (GESMD)**

1. **Symptomatic anemia**
   - Yes: Probability to respond to ESAs
     - Intermediate or high: ESAs ± G-GSF
     - Low: del(5q)
       - Positive: Lenalidomide
       - Negative: BSC or Clinical trial or Second-line approaches in patients failing or losing response:
         - AZA
         - ATG
         - Allo-HSCT
         - lenalidomide
   - No: Close monitoring
2. **Clinical changes or progression**
   - Yes: Re-evaluate strategy
   - No: Watchful waiting strategy
Treatment modalities for MDS
Erythropoiesis stimulating agents (ESAs) (1)

- ESAs are considered first-line treatment for symptomatic anemia of lower-risk MDS patients.
  - Erythroid response rate (IWG criteria) 20 – 70%
  - Median response duration: 18 – 24 months
  - No effect on AML risk
  - No increase risk of DVT reported
  - Potential survival benefit (especially in patients with low transfusion requirements and responders)
Impact of EPO + G-CSF on overall survival of MDS patients (Nordic MDS Study Group and University of Pavia)

A

Overall series

Probability of Survival

EPO-G treated
Untreated

HR = 0.61
(95% CI, 0.44-0.83)
P = .002

Time (years)

< 2 pRBC/month

Probability of Survival

EPO-G treated
Untreated

HR = 0.44
(95% CI, 0.29-0.69)
P < .001

Time (years)


B

Probability of Freedom of AML

EPO-G treated
Untreated

HR = 0.89
(95% CI, 0.52-1.52)
P = .66

Time (years)

C

Probability of Freedom of AML

EPO-G treated
Untreated

HR = 0.67
(95% CI, 0.45-1.66)
P = .67

Time (years)
Treatment modalities for MDS
Erythropoiesis stimulating agents (ESAs) (2)

- Responses usually seen in first 12 weeks
- A dose effect seems to be present
- Darbepoetin and epoetin seem to give similar responses at equipotent doses
- A substantial proportion of patients failing ESAs (16 – 50%) respond to the addition of G-CSF
- Endogenous serum EPO level and RBC transfusion requirements are strongly associated with likelihood and duration of response (Nordic MDS Study group model)
Treatment guidelines for use of ESAs in MDS

- ESAs should be used according to the Nordic MDS study group predictive model of response.\(^1\),\(^2\)
- Use of ESAs in patients with both pejorative criteria (≥ 2 RBC units per month and EPO endogenous level ≥ 500 UI/L) is not recommended.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 points</th>
<th>1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC transfusion requirements</td>
<td>&lt; 2 units/month</td>
<td>≥ 2 units/month</td>
</tr>
<tr>
<td>Serum EPO level</td>
<td>&lt; 500 U/L</td>
<td>≥ 500 U/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Response rate</th>
<th>Response duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>74%</td>
<td>24 months</td>
</tr>
<tr>
<td>1</td>
<td>23%</td>
<td>23 months</td>
</tr>
<tr>
<td>2</td>
<td>7%</td>
<td>3 months</td>
</tr>
</tbody>
</table>

The 5q- syndrome

- 3-4% of all MDS
- Female preponderance
- Macrocytic anemia
- Thrombocytosis
- Hypolobated megakaryocytes
- Isolated interstitial deletion of 5q
- Indolent course (?)

Treatment modalities for MDS
Lenalidomide in lower risk MDS with del(5q) and RBC transfusion dependence

- MDS with del(5q) are specially sensitive to lenalidomide
  - RBC transfusion independence (RBC-TI): 43 – 67%
  - Cytogenetic response: 25 – 73% (complete, 16 – 45%)
  - Median duration of RBC-TI > 2 years
- RBC-TI higher with 10 mg/d x 21 – 28 d than with 5 mg/d
- Most common grade 3 -4 adverse events
  - Neutropenia: 55 – 75%
  - Thrombocytopenia: 33 – 44%
Treatment modalities for MDS
Long-term outcome after lenalidomide in lower risk MDS with del(5q) and RBC transfusion dependence

Potential benefit in overall survival for responders

Treatment modalities for MDS
Long-term outcome after lenalidomide in lower risk MDS with del(5q) and RBC transfusion dependence

Three retrospective comparative studies using different methodology have not shown any significant effect on AML risk

Sánchez-García J, et al. (sumbitted)
Therapeutic algorithm for higher-risk MDS patients (GESMD)

1. **HLA typing**
   - Yes
     - **Donor search**
     - Yes
       - **Donor**
       - **Cytogenetics**
         - Yes
           - **BM blasts**
           - ≤ 10%
             - **Allo-HSCT or AZA followed by allo-HSCT or CT followed by allo-HSCT**
           - > 10%
             - **AZA followed by allo-HSCT or CT followed by allo-HSCT**
         - No
           - **AZA**
     - No
       - **AZA**
         - ** Failure**
           - **CT or Clinical trial**
   - No
     - **Candidate to Intensive treatment**
     - **Yes**
       - **Donor**
       - **BM blasts**
         - Yes
           - **Allo-HSCT**
         - No
           - **CT or AZA**
     - No
       - **AZA**
Treatment modalities for MDS
Hypomethylating drugs: azacitidine

Log-Rank  $p=0.0001$
HR = 0.58 [95% CI: 0.43, 0.77]

Difference: 9.4 months

Treatment modalities for MDS
Hypomethylating drugs

- Azacitidine should be considered as first-line treatment in higher-risk MDS not considered candidates for intensive treatment.

- Azacitidine should also be considered as first-line treatment in higher-risk patients who are candidates to intensive treatment but lack an appropriate donor for allo-SCT (preferable to AML chemotherapy in patients aged over 65 years or with comorbidity, and in those presenting high-risk cytogenetics)
Treatment modalities for MDS
AML-type chemotherapy

Long term results

Candidates

- Patients with higher probability of long-term DFS (30%):
  - Age < 60 yr
  - No comorbidity
  - Favorable cytogenetics

Treatment modalities for MDS
Allogeneic SCT

- Allo-SCT is the only proven curative modality for MDS and should be considered as first-line treatment in higher-risk MDS considered candidates for intensive treatment.

- Results have improved despite greater use of MUD transplants and older patient age

- Key questions under debate

- Access to transplant has increased but still limited to a minority of MDS patients (~ 10%)
Final comments

- Anemia has great relevance in MDS
- Despite great advances in the last decade, treatment remains largely unsatisfactory
- Until more targeted, active, and less toxic therapies become available risk-adapted treatment will continue to be essential
- Patients must be included in clinical trials whenever possible