The role of growth factors myelodysplastic syndromes: what is new?

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Priorities of therapeutic interventions in patients with MDS according to disease stage
Over two-thirds of the newly diagnosed MDS patients have lower-risk disease

IWG-PM database (n = 7,012)

- Low: 40%
- Int-1: 16%
- Int-2: 7%
- High: 37%

IWG-PM, International Working Group for Prognosis in MDS.

Italian registry for MDS: Age distribution and presence of Comorbidities

(n = 1,617)

- Age distribution:
  - ≤ 60: 194 patients (12%)
  - 61–70: 430 patients (27%)
  - 71–80: 670 patients (42%)
  - > 80: 301 patients (19%)

(n = 388)

- Presence of comorbidities (CIRS):
  - Grade 0–2: 142 patients (37%)
  - 1: 99 patients (37%)
  - 2: 77 patients (20%)
  - > 2: 70 patients (18%)

63% with comorbidities (CIRS)

Improving cytopenias

**Anaemia**
- 2/3 of MDS pts
- 50% with Hb < 10 g/dL
- Best supportive care
- ESAs

**Neutropenia**
- G-CSF / GM-CSF

**Thrombocytopenia**
- Thrombopoietin receptor agonists

ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor.
Erythropoiesis-Stimulating Agents Treatment in MDS

- Can induce $\uparrow$ Hb and $\downarrow$ blood transfusions
  - Erythroid response (ER) rates: 45-73% in ESA-naïve MDS pts
  - Median time to ER: 5 weeks (range, 4-9 weeks)
  - Duration of response: from 8 to more than 48 months
- May have a favourable survival impact in MDS
- Some of the studies reported improved quality of life
- ESMO, ASCO, ASH, ELN, NCCN guidelines
Erythropoiesis-Stimulating Agents Treatment in MDS

To whom?
Which dose/regimen?
For how long?

What factors should be considered when deciding on ESA therapy?

Predictive variables for an ESA response in MDS

**Biological**
- IPSS Low or Int-1
- diagnosis of refractory anaemia
- EPO levels < 500 mIU/mL
- marrow blast < 10%
- normal karyotype
- short duration of disease

**Clinical**
- transfusion independence
- short duration of disease

Del(5q) (+/- 10% of patients with low-risk MDS) ➔ Lenalidomide frequently induces transfusion independence

### Treatment Response Score

<table>
<thead>
<tr>
<th>Serum EPO (U/L)</th>
<th>Score</th>
<th>Transfusion requirement (pRBC/month)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>+2</td>
<td>&lt; 2</td>
<td>+2</td>
</tr>
<tr>
<td>100-500</td>
<td>+1</td>
<td>≥ 2</td>
<td>-2</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>-3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MDS IPSS
- Low or int-1
- Hb < 10g/dL

### Response Probability
- Score: 4
  - Very Good
- Score: 3
  - Good
- Score: -1;+1
  - Intermediate
- Score < -1
  - EPO therapy NOT recommended

### Treatment Response Criteria (responses must last at least 8 weeks)
- Hb increase by 1.5 g/dL
- Relevant reduction transfusion (≥ 4U/8weeks)
- Only RBC transfusions given for Hb of 9.0 g/dL pretreatment

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Marta Riva et al. Blood 2017;130:2981
**Erythropoiesis-Stimulating Agents Treatment in MDS**

Which dose/regimen?

<table>
<thead>
<tr>
<th>Epoetin alfa:</th>
<th>Darbepoetin alfa:</th>
</tr>
</thead>
<tbody>
<tr>
<td>40,000 units once per week</td>
<td>150-300 mcg every week</td>
</tr>
<tr>
<td>40,000 units twice a week</td>
<td>500 mcg every 2-3 weeks</td>
</tr>
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</table>

Erythropoiesis-Stimulating Agents Treatment in MDS

For how long?

- It will take about 12 weeks before concluding that ESA therapy is ineffective.
- Transfusions may be needed to manage symptoms while awaiting an ER.
- ESAs should not be continued > 6-9 months if no response is observed.

ER, erythroid response
G-CSF, granulocyte colony-stimulating factor

Weekly epoetin alfa in low-risk MDS patients

Patients and study design

• Open-label, uncontrolled study, n = 133
• Loading dose: 80,000 IU/week for 4 weeks *(40,000 IU twice a week)*
• In non-responders, continue loading dose for 4 weeks
• Maintenance: epoetin alfa 40,000 IU/week s.c. up to 24 weeks

<table>
<thead>
<tr>
<th>Baseline status</th>
<th>Patients, n</th>
<th>Patients, %</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion independent</td>
<td>79</td>
<td>8.84 ± 0.81</td>
<td></td>
</tr>
<tr>
<td>Transfusion dependent</td>
<td>54</td>
<td>8.19 ± 1.20</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RA, refractory anaemia; RAEB, RA with excess blasts; RARS, RA with ringed sideroblasts.
Nearly all transfusion-independent patients (n = 78) remained transfusion independent during 8 weeks of epoetin alfa treatment.

Erythroid response rate:
Overall: 68%
Transfusion-independent patients: 74%
Transfusion-dependent patients: 59%

Erythroid response to epoetin alfa is higher and of longer duration in transfusion-independent patients.
EPO vs. EPO + G-CSF to treat anaemia in low-risk MDS

- Retrospective study
- 30 MDS patients with < 10% bone marrow blasts
- 37% transfusion dependent
- Randomized: EPO 30,000 U/w versus EPO + G-CSF 600 µg/w

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EPO</th>
<th>EPO + G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>40%</td>
<td>73%</td>
</tr>
<tr>
<td>Transformation to AML</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Addition of G-CSF to EPO in non-responders induced a response in 4/9 (45%) pts

Recommendations for the use of ESA and G-CSF combined

- Pts not heavily RBC transfusion dependent (< 2 units/month)
- Serum EPO < 500 mIU/mL
- Who have not responded to ESAs alone

When ring sideroblasts are present, MDS patients will not respond to erythropoietin alone but may respond to EPO + G-CSF
Prolonged survival of MDS patients treated with ESAs

![Graph showing survival rates over time for MDS patients treated with ESAs. The graph demonstrates a significant survival benefit for patients who respond to EPO treatment compared to those who do not, with a p-value of <0.001.]
EPO + G-CSF therapy and AML

HR = 0.89 (95% CI: 0.52–1.52)
p = 0.66

Probability of freedom from AML, %

Time, years

EPO-G treated
Untreated
EPO + G-CSF in patients with lower-risk MDS: impact on overall survival

Increased OS was observed in patients with IPSS Low-risk MDS ($p = 0.033$) but not in patients with higher-risk MDS ($p = \text{n.s.}$).

## Darbepoetin in MDS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients, n</th>
<th>Dose/week</th>
<th>Response rate, %</th>
<th>Prognostic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stasi (2005)</td>
<td>53</td>
<td>150 μg</td>
<td>45</td>
<td>EPO &lt; 200 IU/L</td>
</tr>
<tr>
<td>Musto (2005)</td>
<td>37</td>
<td>150 μg</td>
<td>40.5</td>
<td>EPO &lt; 100 IU/L, No transfusion, Blasts &lt; 5%</td>
</tr>
<tr>
<td>Giraldo (2006)</td>
<td>69</td>
<td>150 μg</td>
<td>55 (30 major, 25 minor)</td>
<td>ESA naive</td>
</tr>
<tr>
<td>Mannone (2006)</td>
<td>63</td>
<td>300 μg</td>
<td>71 (55 major, 16 minor)</td>
<td>EPO &lt; 200 IU/L, No transfusion</td>
</tr>
<tr>
<td>Gabrilove (2008)</td>
<td>ESA naive: 144, Prior ESA: 62</td>
<td>500 μg/3 weeks (every 2 weeks in poor responders)</td>
<td>71 (49 major, 22 minor) 44 (26 major, 18 minor)</td>
<td>ESA naive, EPO &lt; 100 IU/L</td>
</tr>
</tbody>
</table>
ARCADE Study of Darbepoetin alfa for the Treatment of Anemia in Patients With MDS

Phase 3, Randomized, Double-blind, Placebo-Controlled

**Screening (n = 226)**

Main eligibility criteria:
- IPSS low-/int-1–risk
- Hb ≤ 10 g/dL
- Low transfusion burden\(^a\)
- EPO ≤ 500 mU/mL
- ESA-naïve

**Randomization 2:1 (N = 147)**

- Darbepoetin alfa 500 mcg Q3W (n = 97)
- Placebo Q3W (n = 49)

**Active Treatment**

Darbepoetin alfa 500 mcg Q3W (Could increase from Q3W to Q2W from week 31 on)

**End of blinded treatment**

**Long-term follow-up for survival and AML evolution**

**2 weeks  0  24 weeks  48 weeks  84 weeks**

**Objective:** To assess the reduction in RBC transfusions and safety

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\(^a\)Low transfusion burden was defined as < 4 RBC transfusion units in each of 2 consecutive 8-week periods before randomization.

\(^b\)One patient did not receive darbepoetin alfa; serum EPO was ≤ 500 mU/ml locally but > 500 mU/ml centrally, so the patient was withdrawn. 

ARCADE Study: Results

- Transfusion incidence from weeks 5–24 was significantly lower with darbepoetin alfa (36.1% (35/97) versus placebo versus 59.2% (29/49), P = 0.008)
- Erythroid response rates increased significantly with darbepoetin alfa (14.7% (11/75 evaluable) versus 0% (0/35 evaluable), P = 0.016).
- In the 48-week open-label period, dose frequency increased from Q3W to Q2W in 81% (102/126) of patients
The overall rate of AML progression was 2.2%; median time to AML progression was not reached in either treatment group.

**ARCADE Study: Time to AML Progression**

- **PBO (n = 46)**
- **DA (n = 95)**

Log-rank test (adjusted): $P = 0.9781$
ARCADE Study: Time to Death

- 41 deaths occurred on study:
- 27 (28%) in the darbepoetin alfa group and 14 (29%) in the placebo group
- Most died during long-term follow-up (darbepoetin alfa, 93%; placebo, 79%)
Recommendations for ESA dose and iron supplementation

• ESA schedule able to the maintain Hb between 10 and 12 g/dL

• If the patient responds to ESA treatment, an attempt should be made to reduce the dose (or the frequency of administration)

• During ESA treatment, iron supplementation should be considered
  —for patients with a transferrin saturation lower than 20%

ESA treatment does not increase risk of thrombosis in patients with MDS

212 cases of deep vein thrombosis in 5,673 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ESA</td>
<td>1.21</td>
<td>0.60–2.43</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>4.60</td>
<td>2.29–9.23</td>
</tr>
<tr>
<td>Central venous catheter placement</td>
<td>6.47</td>
<td>2.37–17.62</td>
</tr>
</tbody>
</table>

Emerging agents as treatment for anemia in patients with low-risk MDS

Positive regulator of RBC production
**EPO**

Negative regulator of RBC production
**TGF-β superfamily ligands**

**SCF**, **IL-3**, **EPO**

**Sotatercept** (ACE-011)
- Extracellular domain of ActRIIA
- Fc domain of human IgG1 antibody

**Luspatercept** (ACE-536)
- Modified extracellular domain of ActRIIB
- Fc domain of human IgG1 antibody

**Galunisertib**

**Proliferation**

**500 cells**

**8–64 cells**

**BFU-E** → **CFU-E** → **Pro E** → **Baso E** → **Poly E** → **Ortho E** → **Reticulocyte** → **RBC**

**Differentiation/maturation**

**Baso E**, basophilic erythroblast; **EPO**, erythropoietin; **IL-3**, interleukin 3; **Ortho E**, orthochromatic erythroblast; **Poly E**, polychromatic erythroblast; **Pro E**, proerythroblast; **SCF**, stem cell factor.
**TGF-β family members regulate haemopoiesis**

ALK, activin-like kinase receptor; GDF, growth differentiation factor; TIF transcriptional intermediary factor.

ALK4 Activin receptor ligands, GDFs

TGF-β family members

Transphosphorylated TβR complex (ALK5)

Luspatercept

Galunisertib

Phosphorylated SMAD2/3 complex

SMAD6/7

SMAD2

SMAD3

SMAD4

Inhibition of proliferation

Altered erythroid differentiation
Ineffective haemopoiesis

Inhibition of proliferation

Galunisertib
Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis

**Mechanism of action of Luspatercept**

- **Luspatercept**: first-in-class erythroid maturation agent
  - Blocks aberrant Smad2/3 signaling to augment late-stage erythropoiesis
  - Promising clinical activity in lower-risk MDS patients with anemia\(^1\)

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MEDALIST: Study Design

International, randomized, double-blind, placebo-controlled phase III trial

Randomized 2:1

- Patients ≥ 18 yrs of age
- Non-del(5q) MDS
- Ring sideroblasts (WHO 2016 criteria)
- IPSS-R risk: very low, low, or intermediate
- Refractory, intolerant, or ineligible for ESAs
- RBC transfusion dependent (N = 229)

Luspatercept
1.0 mg/kg* SC Q3W for ≥ 24 wks (n = 153)

Placebo
SC Q3W for ≥ 24 wks (n = 76)

*Could be titrated up to 1.75 mg/kg if needed.

Treatment continued until lack of clinical benefit or PD

Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24

Secondary endpoints: RBC TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

### MEDALIST: Efficacy

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC TI ≥ 8 wks in Wks 1-24</td>
<td>37.9</td>
<td>13.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>mHI-E* ≥ 8 wks in Wks 1-48</td>
<td>58.8</td>
<td>17.1</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>▪ Hb increase of ≥ 1.5 g/dL</td>
<td>69.6</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

*Defined as transfusion reduction of ≥ 4 units/8 wks or mean hemoglobin increase ≥ 1.5 g/dL/8 wks in absence of transfusions

Among primary endpoint responders, the median duration of RBC TI response was 30.6 wks in the luspatercept arm vs 13.6 wks in the placebo arm
Conclusions

Erythropoiesis-Stimulating Agents Treatment in MDS

Right Patient
Right Dose
Right time
Thank you

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