Como uma ótima terapia de suporte salva vidas?

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Over two-thirds of the newly diagnosed MDS patients have lower-risk disease

IWG-PM database (n = 7,012)

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

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

Registry for MDS

Italian

(n = 1,617)

- Patients: 194 (12%), 430 (27%), 670 (42%), 301 (19%)

Italy (n=840) and Germany (n=504)

- Overall incidence: 4.4 per 100,000

- Age at Diagnosis (Yrs)
  - 0.2 < 40
  - 0.8 40-49
  - 2.5 50-59
  - 9.2 60-69
  - 27.1 70-79
  - 49.8 ≥ 80

Italian registry for MDS: presence of Comorbidities

63% with comorbidities (CIRS) (n = 388)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Grade 0–2</th>
<th>1</th>
<th>2</th>
<th>&gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>142</td>
<td>99</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Percentage</td>
<td>37%</td>
<td>37%</td>
<td>20%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Has Supportive Care for MDS Improved Over Time? Unfortunately, Not . . .

Dusseldorf registry survival data
(N = 3058; 2449 received Best Supportive Care only)

Cumulative Survival

Survival in Mos

Yr of Diagnosis
- 1970-1975
- 1975-1980
- 1980-1985
- 1985-1990
- 1990-1995
- 1995-2000
- 2000-2005

$P = .5742$
Prolonged survival of MDS patients treated with ESAs

Time since diagnosis or recombinant EPO treatment (years)

Patients alive (%)

- EPO response
- EPO no response
- IMRAW

p < 0.001
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 ($p = \text{n.s.}$)
Iron Chelation Therapy and Survival in MDS

- OS significantly better for patients who received iron chelation therapy
- Results consistent across all subgroups analyzed (IPSS low and intermediate 1, sex, age)

Median survival: 63 mos (whole group)
115 vs 51 mos ($P < .0001$)

Priorities of therapeutic interventions in patients with MDS according to disease stage

**Low-risk MDS**
1. Improvement of cytopenia(s)
2. Tolerability of a given treatment
3. Delay disease progression
4. Cure

**High-risk MDS**
1. Delay disease progression
2. Reduction of disease burden
3. Tolerability of a given treatment
4. Quality of life
Improving cytopenias in patients with MDS

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

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

- **Thrombocytopenia**
  - Thrombopoetin receptor agonists

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

- Can induce ↑ Hb and ↓ blood transfusions
  - Erythoid 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

**CLINICAL GUIDELINES**

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

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

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

Del(5q) (+/- 10% of patients with low-risk MDS)

Lenalidomide frequently induces transfusion independence
Refining Hellström-Lindberg Score (Revised HLS): Which Patients Could Benefit from Standard Dose EPO?

### Treatment Response Criteria (responses must last at least 8 weeks)
- Hb increase by 1.5 g/dL
- Relevant reduction transfusion

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

**Response Probability**

- **Score: 4**
  - MDS IPSS
  - Low or int-1
  - Hb < 10g/dL
  - Very Good

- **Score: 3**
  - Good

- **Score: -1;+1**
  - Intermediate

- **Score < -1**
  - EPO therapy NOT recommended

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>
</tbody>
</table>

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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 (60% transfusion independent [TI])
- 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

Nearly all TI pts (n = 78/79) remained TI 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 TI pts

Recommendations for the use of ESA and G-CSF combined

- Pts not heavily RBC transfusion dependent (< 2 units/month)
- Serum EPO < 500 U/L
- 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

Erythroid response: ESAs + growth factors

High-dose ESA alone usually more effective than lower doses combined with G-CSF

Meta-analysis of 15 MDS trials

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>EPO (30-40K/w)</th>
<th>EPO+G-CSF</th>
<th>EPO (60-80K/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid Response</td>
<td>49%</td>
<td>51%</td>
<td>64%</td>
</tr>
<tr>
<td>Major Erythroid Responses</td>
<td>27%</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>(increase Hb ≥ 2 g/dL and/or complete TI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TI, transfusion independence

**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)\(^b\)
- Placebo Q3W (n = 49)

**End of blinded treatment**

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

**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.

In the 48-week open-label period, dose frequency increased from Q3W to Q2W in 81% (102/126) of patients.

### ARCADE Study: Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>darbepoetin alfa (n=97)</th>
<th>placebo (n=49)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion incidence from weeks 5–24</td>
<td>36.1% (35/97)</td>
<td>59.2% (29/49)</td>
<td>0.008</td>
</tr>
<tr>
<td>Erythroid response rates</td>
<td>14.7% (11/75 evaluable)</td>
<td>0% (0/35 evaluable)</td>
<td>0.0016</td>
</tr>
</tbody>
</table>


Recommendations for ESA dose and iron supplementation

• ESA schedule able to 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>

Serum Ferritin Level Is Predictive of Survival in MDS


Probability

Ferritin < 1000 µg/L
Ferritin ≥ 1000 µg/L

OS

Probability

Yrs From Diagnosis

$P < .0001$
Prospective Chelation Study in Lower-Risk MDS: 48-Mo Update—OS

- 5-yr noninterventional registry study of 599 patients with lower-risk MDS and transfusional iron overload treated with or without chelation
- At 48 mos, chelated patients had significantly longer OS vs nonchelated

**Mediation OS From Diagnosis, Mos**
- Nonchelated (n = 330): 48.7 mos
- Chelated (n = 269): 96.8 mos
- Chelated ≥ 6 mos (n = 202): 102.5 mos

*P < .0001 for chelated vs nonchelated*
TELESTO Study Design

- Multicenter, randomized, double-blind phase II trial
- To evaluate efficacy/safety of the deferasirox vs placebo in low-/intermediate-risk MDS with iron overload

Randomized 2:1; stratified by IPSS (low vs intermediate 1), geographic region (Asian vs non-Asian)

- IPSS low-risk/intermediate 1–risk MDS
- ECOG PS ≤ 2
- Serum ferritin > 1000 ng/mL
- Transfusion > 15 pRBC units
- LVEF ≥ 50%
- CrCl ≥ 40 mL/min  \( (N = 225) \)

Deferasirox
10-40 mg/kg QD based on dosing guidelines  \( (n = 149) \)

Placebo
10-40 mg/kg QD based on dosing guidelines  \( (n = 76) \)

- Composite primary endpoint: EFS, defined as time from randomization to death or first documented nonfatal event (worsened cardiac function, hospitalization for CHF, impaired liver function, liver cirrhosis, AML transformation)
- Secondary endpoints: OS, serum ferritin level increase, hematologic (erythroid) response, endocrine function (thyroid and glycemic control), safety

**TELESTO: EFS (Primary Endpoint)**

Risk of EFS event reduced by 36.4% with deferasirox vs placebo

<table>
<thead>
<tr>
<th>EFS Outcome</th>
<th>Deferasirox (n = 149)</th>
<th>Placebo (n = 76)</th>
<th>HR From Cox Model (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>62 (41.6)</td>
<td>37 (48.7)</td>
<td>0.636 (0.42-0.96; log-rank exploratory)</td>
</tr>
<tr>
<td>Median EFS, days (95% CI)</td>
<td>1440 (1167-1559)</td>
<td>1091 (820-1348)</td>
<td>$P = .015$</td>
</tr>
<tr>
<td>3-yr EFS, %</td>
<td>61.5</td>
<td>47.3</td>
<td></td>
</tr>
</tbody>
</table>

*-*Cox model and log-rank test both stratified by IPSS risk category and geographic region.

Treatment for anemia in patients with low-risk MDS: Emerging agents

- **Positive regulator of RBC production**
  - EPO

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

**Diagram:**
- BFU-E → CFU-E → Pro E → Baso E, Poly E, Ortho E, Reticulocyte → RBC
- SCF, IL-3, EPO (EPO-responsive) → EPO (EPO-dependent)

**Key Points:**
- 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.
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.

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

Take Home Message

Best Supportive Care for MDS Save Life? Unfortunately, Not But

Erythropoiesis-Stimulating Agents Treatment in MDS

Right Patient
Right Dose
Right time

Priorities in low-risk MDS

1. Improvement of cytopenia(s)
   - Less transfusions
   - Less iron overload

2. Tolerability of a given treatment
   - Quality of life

3. Delay disease progression
   - Improve survival

4. Cure
Obrigado

Rodolfo Delfini Cançado
rdcan@uol.com.br
MDS Patients Who Are Likely to Benefit Most From Management Iron Overload

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion status</td>
<td>▪ Received &gt; 20 RBC transfusions</td>
<td>▪ Transfusion dependent, requiring 2 units/mo for &gt; 1 yr</td>
</tr>
<tr>
<td></td>
<td>▪ Continuing transfusions</td>
<td></td>
</tr>
<tr>
<td>Serum ferritin level</td>
<td>▪ &gt; 2500 μg/L</td>
<td>▪ 1000 μg/L</td>
</tr>
<tr>
<td>MDS risk</td>
<td>▪ IPSS: low or intermediate 1 risk</td>
<td>▪ IPSS: low- or int 1</td>
</tr>
<tr>
<td></td>
<td>▪ WHO: RA, RARS and 5q</td>
<td>▪ WHO: RA, RARS and 5q-</td>
</tr>
<tr>
<td>Patient profile</td>
<td>▪ Candidates for allografts</td>
<td>▪ Life expectancy &gt; 1 yr and no comorbidities that limit progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ A need to preserve organ function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Candidates for allografts</td>
</tr>
</tbody>
</table>

Deferasirox Black Box Warning

Deferasirox is contraindicated in patients with

• Creatinine clearance < 40 mL/min or
  serum creatinine > 2 times the age-appropriate ULN

• Poor performance status and high-risk MDS or advanced malignancies
Historical time scale of registration of therapeutic agents for MDS in the EU and US

**FDA**
- 2000: Azacitidine
- 2005: Decitabine
- 2010: Lenalidomide
- 2015: Deferasirox
- 2020: Luspatercept (?)

**EMA**
- 2000: Deferasirox
- 2005: Azacitidine
- 2010: Lenalidomide
- 2015: Epoetin alpha
- 2020: Luspatercept (?)

Haematological responses with deferasirox as iron chelation: EPIC

Symptomatic Low-Risk MDS

Supportive care including transfusion support and iron chelation

- **Thrombocytopenia**
  - TPO-RA*
    - Failure
    - HMA*
      - No
        - LEN
          - Failure
        - Yes
          - LEN*
            - Failure
          - Allo-HSCT
            - Clinical trial
      - Allo-HSCT
      - Clinical trial

- **Anemia in del(5q)**
  - sEPO >500 and RBC-TD
    - mTP53
      - Failure
      - Clinical trial
  - sEPO ≤500
    - ESA +/- G-CSF
      - Failure
      - HMA*
        - LEN
          - LEN*
            - Failure
          - Allo-HSCT
            - Clinical trial
      - Clinical trial

- **Anemia in non del(5q)**
  - sEPO >500
    - ESA +/- G-CSF
      - Failure
      - mSF3B1
      - Hypoplastic
        - LUSP*
          - ATG/CsA*
            - Failure
      - Clinical trial
  - sEPO ≤500
    - ESA +/- G-CSF
      - Failure
ELN guidelines: therapeutic options for IPSS Low-risk MDS

IPSS Low risk

- Asymptomatic cytopenia
  - Watchful waiting
  - sEPO < 500 mU/mL and/or < 2 U RBC/month
  - rHuEPO ± G-CSF
  - Lenalidomide (within prospective registry)

- Symptomatic anaemia
  - del5q
  - sEPO ≥ 500 mU/mL and ≥ 2 U RBC/month
  - RBC transfusion and ICT
  - sEPO < 500 mU/mL and/or < 2 U RBC/month
  - rHuEPO ± G-CSF

- Age < 60 years, BM blasts < 5%, normal cytogenetics, transfusion dependence (hypocellular BM)

ELN, European LeukemiaNet; sEPO, serum erythropoietin; rHuEPO, recombinant human erythropoietin; RBC, red blood cells.

ELN guidelines: therapeutic options for IPSS Int-1-risk MDS

IPSS Int-1 risk

- < 5% BM blasts, no poor risk cytogenetics, asymptomatic cytopenia
  - Watchful waiting
  - del5q
    - sEPO ≥ 500 mU/mL and ≥ 2 U RBC/month
      - Lenalidomide (within clinical trials or prospective registry)
    - sEPO < 500 mU/mL and/or < 2 U RBC/month
      - rHuEPO ± G-CSF

- Symptomatic anaemia
  - RBC transfusion and ICT
    - sEPO < 500 mU/mL and/or < 2 U RBC/month
      - rHuEPO ± G-CSF

- Age up to 65–70, poor risk cytogenetics or persistent blast increase
  - Age < 60 years, BM blasts < 5%, normal cytogenetics, transfusion dependence (hypocellular BM)
    - Immunosuppressive therapy with ATG
    - Available stem cell donor
  - Age up to 65–70, poor risk cytogenetics or persistent blast increase
    - Allo-SCT
What about G-CSF?
- synergistic effect with ESAs in MDS shown in RCTs
- usually added if no response to ESA alone after 3 months
- no improvement in OS yet seen in RCT for ESA+ G-CSF

ESA+GM-CSF?
- lower response rate
- more toxic in MDS

High-dose ESA alone usually more effective than lower doses combined with G-CSF
- meta-analysis of 15 MDS trials
  - EPO (30–40K U/week) vs EPO+G-CSF or GM-CSF vs High-dose EPO (60–80K U/week)
- ORR-erythroid: 49%, 51%, and 64%, respectively
- major erythroid responses (increase Hb ≥ 2 g/dL and/or complete TI): 27%, 30%, and 45%, respectively

GM-CSF, granulocyte-macrophage colony-stimulating factor; RCT, randomized-controlled trial; TI transfusion independence.

• SELECT patients with a good chance of response
  • lower-risk IPSS (Low/Int-1)
  • low EPO level
  • low transfusion requirements
  • higher Hb levels
• START early, START at high dose
  • if response, then continue but adjust dose to tolerance and need
  • if no response or relapse after initial response, add G-CSF
• STOP if
  • continued lack of response
  • no response to combination in 6–8 weeks
  • relapse of transfusion needs
MDS: treatment NCCN guidelines

**IPSS: Low/Int-1**
**WPSS: Very Low, Low, Int**

Symptomatic anaemia

Serum EPO ≤ 500 mU/mL
- EPO alfa (rHu EPO) ± G-CSF or Darbepoetin alfa ± G-CSF
  - Good probability to respond to immunosuppressive therapy\(^a\)
  - No response
  - Azacitidine/decitabine or Consider lenalidomide or Clinical trial

Serum EPO > 500 mU/mL
- Poor probability to respond to immunosuppressive therapy\(^b\)
  - Antithymocyte globulin, ciclosporin A
  - Azacitidine/decitabine or Consider lenalidomide or Clinical trial

Supportive care as an adjunct to treatment

**del(5q) ± other cytogenetic abnormalities**

Lenalidomide


MDS: treatment NCCN guidelines (cont.)

- **IPSS: Low/Int-1**
- **WPSS: Very Low, Low, Int**

### Symptomatic anaemia
- **Serum EPO ≤ 500 mU/mL**
  - **Supportive care as an adjunct to treatment**
  - **Serum EPO > 500 mU/mL**
    - **Good probability to respond to immunosuppressive therapy**
    - **Poor probability to respond to immunosuppressive therapy**

### del(5q) ± other cytogenetic abnormalities
- **Lenalidomide**

### Other cytogenetic abnormalities
- **EPO alfa (rHu EPO) ± G-CSF**
  - **No response**
  - **Consider lenalidomide or Clinical trial**

### Symptomatic anaemia
- **Serum EPO ≤ 500 mU/mL**
  - **Lenalidomide**
  - **Antithymocyte globulin, ciclosporin A**
  - **Azacitidine/decitabine or Consider lenalidomide or Clinical trial**

- **Serum EPO > 500 mU/mL**
  - **Good probability to respond to immunosuppressive therapy**
  - **Poor probability to respond to immunosuppressive therapy**

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*a* Particularly Low/Int-1 patients aged 60 years or those with hypocellular marrows, HLA-DR15, or PNH clone positivity.

*b* Patients lack features listed in *a*. 

MDS: treatment NCCN guidelines (cont.)

**IPSS: Low/Int-1**  
**WPSS: Very Low, Low, Int**

- **Symptomatic anaemia**
- **Serum EPO ≤ 500 mU/mL**
  - **Serum EPO > 500 mU/mL**
  - **del(5q) ± other cytogenetic abnormalities**
  - **EPO alfa (rHu EPO) ± G-CSF or Darbepoetin alfa ± G-CSF**
  - **Good probability to respond to immunosuppressive therapy**
  - **Poor probability to respond to immunosuppressive therapy**

- **No response**
  - **Lenalidomide**

- **NOC response**
  - **Azacitidine/decitabine or Consider lenalidomide or Clinical trial**
  - **Antithymocyte globulin, ciclosporin A**
  - **Azacitidine/decitabine or Consider lenalidomide or Clinical trial**

---

*a* Particularly Low/Int-1 patients aged 60 years or those with hypocellular marrows, HLA-DR15, or PNH clone positivity.

*b* Patients lack features listed in *a*.

MDS: treatment NCCN guidelines (cont.)

IPSS: Low/Int-1
WPSS: Very Low, Low, Int

- Symptomatic anaemia
  - Serum EPO ≤ 500 mU/mL
    - EPO alfa (rHu EPO) ± G-CSF or Darbepoetin alfa ± G-CSF
      - Good probability to respond to immunosuppressive therapy
      - No response
    - Serum EPO > 500 mU/mL
      - Poor probability to respond to immunosuppressive therapy

- del(5q) ± other cytogenetic abnormalities
  - Lenalidomide

- Patients lack features listed in a.
  - Antithymocyte globulin, ciclosporin A
  - Azacitidine/decitabine or Consider lenalidomide or Clinical trial

- Supportive care as an adjunct to treatment

- No response
  - Azacitidine/decitabine or Consider lenalidomide or Clinical trial


a Particularly Low/Int-1 patients aged 60 years or those with hypocellular marrows, HLA-DR15, or PNH clone positivity.
b Patients lack features listed in a.
A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes (MEDALIST)

A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to the IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects With Ring Sideroblasts Who Require Red Blood Cell Transfusions.

• Study Arms:
  • Experimental: Experimental Arm - Luspatercept (ACE-536) Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks
  • Intervention: Drug: Luspatercept
  • Placebo Comparator: Control Arm: Placebo Subcutaneous injection every 3 weeks
  • Intervention: Other: Placebo
Patients with IPSS Low/Int-1 MDS and overall favourable prognostic factors of response to ESA according to the Nordic score (n = 456)

- In multivariate analysis, IPSS-R, serum EPO, and SF were significantly associated with erythroid response (p < 0.0001, p < 0.0001, p = 0.002, respectively)

Significant dysgranulopoiesis is associated with lower response rate to ESA

- Inversely correlated with ANC ($p = 0.003$)
- Seen in 45% of IPSS Low-risk and 69% of IPSS Int-1-risk patients ($p = 0.003$)
- Correlated with WHO
  - RA 35%, RARS 48%, RAEB-1 60%, RCMD 85%, MDS 5q− 33%; $p < 0.0001$
- More frequent in patients with dysmegakaryopoiesis (73% vs 44%; $p < 0.0001$)
- Independent of Hb level and sEPO

No difference in activity of ESAs

IWG 2006 response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa</td>
<td>56.6</td>
</tr>
<tr>
<td>Epoetin . . .</td>
<td>63.1</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>66.2</td>
</tr>
</tbody>
</table>

N = 403

ESAs: duration of response varies according to level of response

![Graph showing duration of response to recombinant EPO according to IWG 2000 response criteria](graph)

Duration of response to recombinant EPO according to IWG 2000 response criteria

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Patients, n</th>
<th>Median response duration, months</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>168</td>
<td>24.4</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Minor</td>
<td>83</td>
<td>13.8</td>
<td>1.63</td>
<td>1.1–2.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Haematological responses with deferasirox as iron chelation: GIMEMA

Erythroid response

Friedman test $p < 0.0001$

- Upper quartile
- Median
- Lower quartile

pRBC, units/month

Time, months

### Management goals by IPSS: IWG

<table>
<thead>
<tr>
<th>Treatment goal</th>
<th>Low or Int-1 risk</th>
<th>Int-2 or High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical end-point</strong></td>
<td>Haemopoiesis</td>
<td>Survival</td>
</tr>
<tr>
<td>- HI</td>
<td>- Alter natural history</td>
<td></td>
</tr>
<tr>
<td>- Quality of life</td>
<td>- Delay/block progression to AML</td>
<td></td>
</tr>
<tr>
<td><strong>Management considerations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Erythropoiesis-stimulating agent</td>
<td>- AZA-nucleosides</td>
<td></td>
</tr>
<tr>
<td>- Immunomodulatory drug</td>
<td>- Allogeneic stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>- Immunosuppressive therapy</td>
<td>- Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>- AZA-nucleosides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Historical time scale of registration of therapeutic agents for MDS in the EU and US
Therapeutic algorithm in low-risk MDS patients
Standards and perspectives of therapeutic options in patients with MDS
Why is TGF-β signalling activated in MDS?

Negative regulator Smad7 is reduced

SMAD2 **

SMAD7

Controls MDS

RA, refractory anaemia; RAEB; RA with excess blasts; RARS, RA with ringed sideroblasts.

Luspatercept corrects anaemia by promoting late-stage erythropoiesis

Inhibits SMAD2/3 signalling

Normalizes M:E ratio in BM

Increases Hb

WT + TBS

MDS + TBS

MDS + RAP-536

Hb (g/dL)

74%

48%

68%

26%

52%

32%

Erythroid precursors

Non-erythroid cells

* p < 0.001 vs WT + TBS

** p < 0.05 vs MDS + TBS

TBS, tris-buffered saline; M:E, myeloid:erythroid.
Conclusions

• Activin pathway plays an important role in erythropoiesis
  • SMAD2/3 is a downstream transcription factor in that pathway
  • SMAD7 is a negative regulator of SMAD2/3
• SMAD2/3 is significantly increased ineffective haemopoiesis in bone marrow failure states
  • SMAD7 is reduced in MDS, leading to the upregulation of SMAD2/3
• Activin receptor ligant trap technologies such as sotatercept
  • showed promising evidence of clinical activity in this cohort of lower-risk MDS patients who were anaemic and refractory to ESAs
  • is well tolerated in lower-risk MDS patients at the dose levels tested
  • further data is needed with higher dose levels and longer-term treatment exposure of sotatercept
Pathogenesis of ineffective haemopoiesis in MDS: increased SMAD2/3 signalling

Activin receptors, TGF-β

\[ \text{SMAD2} \rightarrow \text{SMAD3} \]

Ineffective haemopoiesis; Low blood counts

ActRII pathway:
(A) ActRII pathway - (B) ActRII pathway inhibition
Eligibility criteria: EPO > 500 U/L or non-responsive/refractory to ESA; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF

Primary efficacy end-points
- LTB < 4 U RBC/8 weeks; Hb < 10 g/dL; Hb increase of ≥ 1.5 g/dL for ≥ 2 weeks
- HTB ≥ 4 U RBC/8 weeks; reduction of ≥ 4 U or ≥ 50% U transfused over 8 weeks

Luspatercept administered s.c. every 3 weeks for 3 months
Erythroid response to epoetin alfa is higher and of longer duration in transfusion-independent patients

**Responders by week and dose**

- 40,000 IU twice a week
- 40,000 IU weekly or twice a week

**Response duration**

- Major response (100% reduction in transfusions in the last 4 weeks)
- Minor response (> 50% and < 100% reduction in transfusions in the last 4 weeks)

Sotatercept and luspatercept act as novel ligand traps for TGF-β superfamily ligands.

Amino acid homology between ECD of sotatercept and luspatercept is ~ 60%

The murine orthologues of these molecules are RAP-011 and RAP-536; extracellular domains are identical, but linked to murine IgG2a Fc domain.
Luspatercept in Ring Sideroblast+ Myelodysplastic Syndrome (MEDALIST): Background

• MDS characterized by ineffective erythropoiesis, anemia requiring lifelong RBC transfusions
  • Anemia treatment is unmet need in lower-risk transfusion-dependent MDS that is refractory to ESAs
• 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\[^1\]
• MEDALIST: randomized, double-blind, placebo-controlled phase III trial evaluating safety and efficacy of luspatercept in pts with very low- to intermediate-risk MDS with ring sideroblasts who require regular RBC transfusions\[^2\]

MEDALIST: Conclusions

• Luspatercept significantly reduced RBC transfusion burden compared with placebo in transfusion-dependent patients with very low- to intermediate-risk MDS with RS
  • Met primary endpoint of improving proportion of patients achieving RBC transfusion independence for ≥ 8 wks in Wks 1-24
  • Significantly more patients achieved RBC transfusion independence for ≥ 12 wks in Wks 1-24 and in Wks 1-48
  • Significantly more patients achieved increase in Hb of ≥ 1.5 g/dL
• Luspatercept significantly improved mHI-E of ≥ 8 wks
• Treatment generally well tolerated
• Investigators conclude that luspatercept may offer new treatment option for transfusion-dependent anemia in lower-risk RS-positive MDS patients
### Key studies of EPO + G-CSF in MDS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients, n</th>
<th>Response rate, %</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellström-Lindberg (1998)</td>
<td>71</td>
<td>38</td>
<td>Erythroid response (20% CR) Synergy</td>
</tr>
<tr>
<td>Negrin (1996)</td>
<td>44</td>
<td>48</td>
<td>Erythroid response Synergy</td>
</tr>
<tr>
<td>Remacha (1999)</td>
<td>32</td>
<td>50</td>
<td>Erythroid response Synergy</td>
</tr>
<tr>
<td>Mantovani (2000)</td>
<td>28</td>
<td>61</td>
<td>Response at 12 weeks 61%, at 36 weeks 80% Good prognosis patients</td>
</tr>
</tbody>
</table>

CR, complete response.
Higher doses of epoetin alfa increase response rates

Meta-analysis of erythroid response to ESAs

Higher dosing regimens of epoetin alfa (weekly dose 60–80 KU) correlate with higher response rate

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Response Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose (30–40,000 U/week)</td>
<td>49.0%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Standard dose + G-CSF or GM-CSF</td>
<td>50.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>High dose (60–80,000 U/week)</td>
<td>64.5%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Higher dosing regimens of epoetin alfa correlate with higher response rate.

EPO, erythropoietin; ESA, erythropoietic stimulating agents; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage CSF.
Higher doses of darbepoetin alfa increase response rates

Meta-analysis of erythroid response to ESAs

Higher dosing regimens of darbepoetin alfa (weekly dose 150–300 µg) correlate with higher response rate
Emerging agents as treatment for anemia in patients with low-risk MDS

- **Sotatercept and Luspatercept**
  
  ✓ act as novel ligand traps for TGF-β superfamily ligands

- **Galunisertib**
  
  ✓ is an oral drug that inhibits SMAD2/3 activation

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

For transfusion-dependent low-risk MDS patients without del(5q), there are few effective treatments following ESA failure; lenalidomide can induce transfusion independence in approximately 25%. Immunosuppressive therapy, such as antithymocyte globulin with cyclosporine, should be restricted to select patients.\(^4,5\)

Del(5q) can be detected in approximately 10% of patients with low-risk MDS. Lenalidomide frequently induces transfusion independence in low-risk MDS patients with del(5q).\(^4\)

When ring sideroblasts are present, MDS patients will not respond to erythropoietin alone but may respond to erythropoietin plus G-CSF. Such patients may respond to high dose darbepoetin; it is not clear that G-CSF synergizes with the latter ESA.
ARCADE Study: Results

RBC Transfusion Incidence and HI-E Rates According to IPSS Risk Groups at 24 Weeks

RBC transfusion incidence

<table>
<thead>
<tr>
<th>IPSS Low Risk</th>
<th>IPSS Int-1 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>DA</td>
</tr>
<tr>
<td>% Transfused</td>
<td>% Transfused</td>
</tr>
<tr>
<td>48% (12/25)</td>
<td>71% (17/24)</td>
</tr>
</tbody>
</table>

Achievement of HI-E

<table>
<thead>
<tr>
<th>IPSS Low Risk</th>
<th>IPSS Int-1 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>DA</td>
</tr>
<tr>
<td>% Achieving HI-E</td>
<td>% Achieving HI-E</td>
</tr>
<tr>
<td>0% (0/18)</td>
<td>18% (7/38)</td>
</tr>
</tbody>
</table>

DA, darbepoetin alfa; HI-E, haematologic improvement–erythroid response; int-1, intermediate-1.

Roberto Latagliata et al. Blood 2017;130:4262
Individualize use of ESAs based on benefit-risk ratio for each patient

<table>
<thead>
<tr>
<th>MDS Low or int-1 Hb &lt; 10g/dL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Probability of an erythroid response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>High 74%</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate 23%</td>
</tr>
<tr>
<td>2</td>
<td>Low 7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Serum EPO (U/L)</th>
<th>Transfusion requirement (pRBC per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 500</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>1</td>
<td>≥ 500</td>
<td>≥ 2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eritropoese Normal

- **Eritrócitos**
  - 20-30 bilhões
- **Taxa de produção**
  - ~ 2 milhões/min
- **Vida média**
  - 120 dias
- **Percurso total**
  - cerca de 6 Km
MDS: definition, pathophysiology, and mortality

• Definition
  ✓ haematological clonal diseases characterized by cytopenia(s) and normal or increased bone marrow cellularity (~ 90% of cases) with morphological dysplastic changes in bone marrow and peripheral blood

• Pathophysiology
  ✓ increased apoptosis ➔ ineffective haemopoiesis

• Mortality
  ✓ haemorrhage particularly in the central nervous system
  ✓ infections
  ✓ cardiac failure
Myelodysplastic Syndromes

- A group of malignant hematopoietic disorders characterized by\[^1\]
  - Bone marrow failure with resultant cytopenia and related complications
  - Macrocytic anemia is most common presentation
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000\[^2\]
  - \(\approx\) 10,000/yr in United States (true estimates \(\approx\) 37,000-48,000)
  - Median age: 70 yrs; incidence: 34-47/100,000 > 75 yrs\[^3\]

---

Luspatercept for Treating Anemia in MF

- Open-label, nonrandomized, multicohort phase II trial\[^{1,2}\]

**Treatment:** luspatercept at starting dose of 1.0 mg/kg Q3W x 8 cycles

<table>
<thead>
<tr>
<th>Cohort 1: Anemia only, not currently receiving RBC transfusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2: RBC transfusion–dependent anemia</td>
</tr>
<tr>
<td>Cohort 3A/B: Meeting criteria for Cohort 1 or 2 while on stable dose of ruxolitinib before enrollment</td>
</tr>
</tbody>
</table>

- Primary endpoint: anemia response (Hb increase ≥ 1.5 g/dL from baseline or RBC transfusion independence for ≥ 84 days)

- Phase III trials evaluating luspatercept ongoing in lower-risk MDS (MEDALIST[^3]) and β-thalassemia–associated anemias (BELIEVE[^4])

---

MDS Epidemiology

• Overall incidence: 4.4 per 100,000
The Cardinal Features of MDS

**Patients:**
- Median age: 70-75 yrs
- Previous chemotherapy (alkylators, topoisomerase II inhibitors)
- Previous radiation exposure
- Patients: ~1/2 of patients have abnormal chromosomes, usually numeric anomalies

**Disease features:**
- >95% of patients have cytopenias, most commonly anemia
- Bone marrow usually hypercellular, cells look abnormal ("dysplastic"), blasts may be increased
- ~1/2 of patients have abnormal chromosomes, usually numeric anomalies

**Clinical course:**
- "PreLeukemia"
- Infection, bleeding, complications of anemia (50%)
- AML (25%)
- Death from other causes (25%)
Standards and perspectives of therapeutic options in MDS
Cumulative Incidence of Death Without AML (%)

- BSC: Blue line, 52/114, Gray test $P = .17$
- Decitabine: Yellow line, 67/119

Overall Survival (%)

- MDS $<$ 3 months: Gray line, 101/117, Log-rank test $P = .052$
- MDS $\geq$ 3 months: Red line, 94/116

No. at risk:
- BSC: 58, 33, 16, 8, 4
- Decitabine: 72, 47, 21, 14, 3
- MDS $<$ 3 months: 70, 39, 20, 10, 4
- MDS $\geq$ 3 months: 84, 52, 26, 15, 3
Figure 1. Guidelines from the NCCN, ESMO, and ELN for lower-risk MDS patients. Transfusion dependence is defined as an RBC transfusion need of ≥2 units/month. ATG = antithymocyte globulin; CSA = cyclosporin A; del(5q) = chromosome 5q deletion; ELN = European LeukemiaNet; EPO = erythropoietin; ESMO = European Society for Medical Oncology; G-CSF = granulocyte-colony stimulating factor; ICT = iron chelation therapy; Int = Intermediate; IPSS = International Prognostic Scoring System; IST = immunosuppressive therapy; MDS = myelodysplastic syndromes; NCCN = National Comprehensive Cancer Network; NTD = non-transfusion dependent; RBC = red blood cell; sEPO = serum erythropoietin; TD = transfusion dependent. * Lenalidomide is not licensed for the treatment of lower-risk MDS in the EU. Hypomethylating agents may be considered in special cases (approved in the USA only).
Anemia Management Algorithm 2013: Low- or Intermediate 1–Risk MDS

- Assess potential causes of anemia
- Supplement with iron, folate, vitamin B as needed
- RBC transfusion support for symptomatic patients

EPO ≤ 500 mU/mL; < 2 U RBC/mo

- ESA ± G-CSF
- IST
  - AZA/DAC Lenalidomide Clinical Trial

EPO > 500 mU/mL; RCMD; ≥ 2 U RBC/mo

- ≤ 60 yrs of age, hypocellular marrow, HLA-DR15+, PNH+
- yes
  - AZA/DAC Lenalidomide Clinical Trial
- no
  - IST

Adapted from NCCN. Clinical practice guidelines in oncology. MDS. v.2.2013.
Initial Approach to the Treatment of Anemia in MF

EPO levels

- ADEQUATE ≥ 500 mIU/mL
  - Danazol, others

- INADEQUATE < 500 mIU/mL
  - ESA x 3 mos
  - No response
  - Response

## 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>

The overall rate of AML progression was 2.2%; median time to AML progression was not reached in either treatment group.
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%)

ARCADE Study: Time to Death

Stratification factor for Log-rank test is IPSS score

Log-rank test (adjusted): $P = 0.7822$

Patients with Fatal Event, %

- **DA** (n = 98)
- **PBO** (n = 48)

Patients at risk:

- **PBO**: 48 48 42 41 41 40 38 37 36 36 33 32 31 30 28 22 16 6 2 1 1 0
- **DA**: 98 97 93 90 89 88 86 83 83 81 78 75 75 69 52 27 24 6 3 1 0

Platzbecker U, et al. Slides presented at 23rd European Hematology Association Congress; June 14-17, 2018; Stockholm, Sweden. Abstract EHA-3168. Graph adapted from Reference.
Prospective Chelation Study in Lower-Risk MDS: 48-Mo Update—AML Transformation

- At 48 mos, chelated patients had significantly longer time to AML transformation vs no chelation
  - Percentages of patients who progressed to AML similar in both groups (~7% to 10%)

**Median Time to AML Progression, Mos**
- Nonchelated (n = 330): 45.6
- Chelated (n = 269): 67.6
- Chelated ≥ 6 mos (n = 202): 77.0

\[ P < .0001 \text{ for chelated vs nonchelated} \]
Iron Chelation Therapy in Lower-Risk MDS With Iron Overload

- Chronic transfusions commonly lead to iron overload in patients with MDS\(^1\)

- Iron chelation therapy in lower-risk MDS has been associated with improved OS and other favorable outcomes\(^2-6\)
  - Most studies in this setting are observational registries or retrospective
  - Data from large randomized trials are lacking

**TELESTO: EFS (Primary Endpoint)**

- Risk of EFS event reduced by 36.4% with deferasirox vs placebo
- Most common IRC-confirmed EFS events
  - Deferasirox: AML progression (6.7%), worsening cardiac function (1.3%), hospitalization for CHF (0.7%), impaired liver function (0.7%)
  - Placebo: AML progression (7.9%), hospitalization for CHF (3.9%), worsening cardiac function (2.6%), impaired liver function (1.3%)

<table>
<thead>
<tr>
<th>EFS Outcome</th>
<th>Deferasirox (n = 149)</th>
<th>Placebo (n = 76)</th>
<th>HR From Cox Model (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>62 (41.6)</td>
<td>37 (48.7)</td>
<td>0.636 (0.42-0.96; log-rank exploratory P = .015)</td>
</tr>
<tr>
<td>Median EFS, days (95% CI)</td>
<td>1440 (1167-1559)</td>
<td>1091 (820-1348)</td>
<td></td>
</tr>
<tr>
<td>3-yr EFS, %</td>
<td>61.5</td>
<td>47.3</td>
<td></td>
</tr>
</tbody>
</table>

* Cox model and log-rank test both stratified by IPSS risk category and geographic region.

TELESTO Study Design

To evaluate efficacy/safety of the deferasirox vs placebo in low-/intermediate-risk MDS with iron overload

Screening

Low- or int 1–risk MDS
Serum ferritin
> 1000 µg/L and
< 2500 µg/L

Randomization
(2:1 = Deferasirox/Placebo)

Deferasirox (n = 420)
10 mg/kg/day (1st 2 wks)
20 mg/kg/day (Wks 2-12)
Up to 40 mg/kg/day (after 12 wks)

Placebo (n = 210)
10 mg/kg/day (1st 2 wks)
20 mg/kg/day (Wks 2-12)
Up to 40 mg/kg/day (after 12 wks)

1 yr 2 yrs 3 yrs 4 yrs 5 yrs

IA IA

54% chance to stop the trial depending on IA results

Expected end of study

Interim analysis: At 50% (~ 3 yrs) and 75% of primary composite events (~ 4 yrs)
Addition of EPO to G-CSF Improved OS, But No Effect on AML Transformation

- Analysis of 3 phase II Nordic group trials of patients who received EPO (N = 121)
- Control group who received no EPO (N = 237)
- ESA exposure: 39% erythroid RR
- HR for death: 0.61 (P = .002)
EPO + G-CSF Improves OS in MDS: Comparison of GFM and IMRAW Cohorts

• Major erythroid response in GFM: 40%
  • HR for death: 0.43 ($P < .001$)
A

Overall Survival (%)

- BSC
- Decitabine

Log-rank test $P = .38$

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>BSC</th>
<th>Decitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>99</td>
</tr>
</tbody>
</table>

B

Progression-Free Survival (%)

- BSC
- Decitabine

Log-rank test $P = .004$

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>BSC</th>
<th>Decitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>113</td>
</tr>
</tbody>
</table>

No. at risk:

BSC
- 83
- 62

Decitabine
- 71
- 62
Standards and perspectives of therapeutic options in MDS
E1996 Phase III Trial of EPO ± G-CSF: No Difference in OS

OS by Treatment

<table>
<thead>
<tr>
<th>Treatment, n</th>
<th>Total</th>
<th>Fail</th>
<th>CNSR</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>57</td>
<td>48</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>EPO 150 μ/kg/day</td>
<td>53</td>
<td>38</td>
<td>15</td>
<td>37</td>
</tr>
</tbody>
</table>

Log-rank $P = .28$
What about G-CSF?
- synergistic effect with ESAs in MDS shown in RCTs
- usually added if no response to ESA alone after 3 months
- no improvement in OS yet seen in RCT for ESA+ G-CSF

ESA+GM-CSF?
- lower response rate
- more toxic in MDS

High-dose ESA alone usually more effective than lower doses combined with G-CSF
- meta-analysis of 15 MDS trials
  - EPO (30–40K U/week) vs EPO+G-CSF or GM-CSF vs High-dose EPO (60–80K U/week)
- ORR-erythroid: 49%, 51%, and 64%, respectively
- major erythroid responses (increase Hb ≥ 2 g/dL and/or complete TI): 27%, 30%, and 45%, respectively

GM-CSF, granulocyte-macrophage colony-stimulating factor; RCT, randomized-controlled trial; TI transfusion independence.

Treatment for anemia in patients with low-risk MDS: Emerging agents

Positive regulator of RBC production
EPO

Differentiation/maturation
Negative regulator of RBC production
TGF-β superfamily ligands

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

500 cells → 8–64 cells

SCF, IL-3, EPO → EPO-responsive
EPO-dependent → 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

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.
Summary: practical aspects of ESA use

- SELECT patients with a good chance of response
  - lower-risk IPSS (Low/Int-1)
  - low EPO level
  - low transfusion requirements
  - higher Hb levels
- START early, START at high dose
  - if response, then continue but adjust dose to tolerance and need
  - if no response or relapse after initial response, add G-CSF
- STOP if
  - continued lack of response
  - no response to combination in 6–8 weeks
  - relapse of transfusion needs

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

Conflitos de Interesses
Rodolfo D. Cançado CRM 56697/SP

De acordo com a resolução do Conselho Federal de Medicina nº 1595/2000 e Resolução da Diretoria Colegiada da ANVISA nº 96/2008, eu declaro que:

- Pesquisa Clínica – Como investigador: AstraZeneca, Novartis
- Apresentações científicas – Como palestrante: Novartis, Takeda, Farmoquimica, AstraZeneca, Amgen
- Atividades de Consultoria – Como membro de Advisory Boards: Novartis

Declaro não ter ações em bolsa de valores das empresas supracitadas.

Meus pré-requisitos para participar destas atividades são o intercâmbio científico, a autonomia do pensamento científico, independência de opinião e liberdade de expressão, aspectos estes respeitados pela Novartis.

As informações fornecidas neste material podem incluir recomendações que não constam na bula aprovada de nossos produtos. Estas informações têm o intuito de fornecer a você os dados científicos pertinentes para tirar suas próprias conclusões e para tomar suas próprias decisões. Estas informações não são destinadas à promoção ou recomendação de nenhuma indicação, dose ou outra alegação não incluída na bula do produto. A Novartis não corrobora a promoção de seus produtos de uma forma que não esteja de acordo com suas bulas aprovadas.
MDS: definition, pathophysiology, and mortality

• Definition
  ✓ haematological clonal diseases characterized by cytopenia(s) and normal or increased bone marrow cellularity (~ 90% of cases) with morphological dysplastic changes in bone marrow and peripheral blood

• Pathophysiology
  ✓ increased apoptosis ➞ ineffective haemopoiesis

• Mortality
  ✓ haemorrhage particularly in the central nervous system
  ✓ infections
  ✓ cardiac failure
Serum Ferritin Level Is Predictive of Survival and Risk of AML in MDS

- Development of transfusional iron overload is a significant independent prognostic factor for OS and transformation to AML

LPI enters into cells by unregulated pathways surpassing storage abilities & generating labile cell iron (LCI)

NTBI and LPI are mainly found when TS > 45% and 75%, respectively

NTBI=non-transferrin-bound iron; LPI=labile plasma iron; LCI=labile cytoplasmatic iron; ROS=reactive oxygen species; ST = transferrin saturation

FDA-Approved Agents for Iron Chelation

**Deferoxamine**
- FDA approved: 1968
- Delivery: SQ, IM, IV

[Chemical Structure of Deferoxamine]

**Deferasirox**
- FDA approved: 2005
- Delivery: Oral

[Chemical Structure of Deferasirox]

**Deferiprone**
- FDA approved: 2011
- Delivery: Oral

[Chemical Structure of Deferiprone]
Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis

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\[1\]