EPO and thrombopoietic agents in MDS

14th Annual Course
Anemia, Neutropenia, Thrombosis and Cancer
Madrid, March 6th/7th, 2015

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## Disclosures – Reinhard Stauder

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
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MDS - Clinical relevance

- MDS are one of the most common hematologic malignancies
- Median age at diagnosis is ~75 yrs
- Successful chemo- and/or radiotherapy of a primary tumor results in a growing number of therapy-related MDS (t-MDS)
- Loss of life years and quality of life (QoL) in nearly all patients
- Main clinical problems
  - Cytopenias
    - Anemia in ~90%; Hb < 10g/dL in ~50%; RBC-transfusions in ~80%
    - Thrombopenia (<50 G/l) in ~ 33%
    - Granulopenia (<1.5 G/l) in 5–10%
  - Risk of AML-transformation
# IPSS-R (revision)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Score values</th>
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<td><strong>Cytogenetics</strong></td>
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<td><strong>Blasts BM, %</strong></td>
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<td><strong>Hb (g/dl)</strong></td>
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<td><strong>Platelets (G/l)</strong></td>
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<td><strong>Neutrophils (G/l)</strong></td>
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## Risk groups

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<td>&gt;4.5 – 6</td>
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<td>&gt;6</td>
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## Cytogenetic risk groups

<table>
<thead>
<tr>
<th>Prognostic subgroup</th>
<th>Cytogenetic Aberration</th>
<th>Median survival; yrs</th>
<th>Median AML-evolution 25%; yrs</th>
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<tr>
<td>Very good</td>
<td>-Y, del(11q)</td>
<td>5.4</td>
<td>NR</td>
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<tr>
<td>Good</td>
<td>Normal, del (5q), del (12p), del (20q), double including del (5q)</td>
<td>4.8</td>
<td>9.4</td>
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<tr>
<td>Intermediate</td>
<td>del (7q), +8, +19, i(17q), any other single or double independent clones</td>
<td>2.7</td>
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<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities</td>
<td>1.5</td>
<td>1.7</td>
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<tr>
<td>Very poor</td>
<td>Complex: &gt;3 abnormalities</td>
<td>0.7</td>
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[www.ipss-r.com/](http://www.ipss-r.com/)
### IPSS-R – survival related to age

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<th>Age groups, y</th>
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<td>&gt;70-80</td>
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<td>&gt;80</td>
<td>5.2</td>
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*Survival (Median, years)*

[Greenberg P et al., Blood, 2012](http://www.ipss-r.com/)
## IPSS-R – survival related to age

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<tr>
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<td>Intermediate</td>
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<tr>
<td>All</td>
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<td>&gt;70-80</td>
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<td>&gt;80</td>
<td>5.2</td>
<td>3.2</td>
<td>1.8</td>
<td>1.5</td>
<td>0.7</td>
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*Survival (Median, years)*

**Low-risk**

**High-risk**

Greenberg P et al., Blood, 2012
## WPSS-R

### Characteristics

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<tr>
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<tr>
<td><strong>Cytogenetics (IPSS-R)</strong></td>
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<td><strong>Hb-levels</strong></td>
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<td>Hb &gt;8 g/dl f</td>
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### Risk groups

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<tr>
<td>High</td>
<td>4-5</td>
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<tr>
<td>Very high</td>
<td>&gt;5</td>
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**OS**

**LFS**

*Della-Porta MG et al., Leukemia, 2015, in press*
Transfusion frequency impacts outcome in MDS

OS
(HR = 1.36; p < 0.001)

Leukaemia-free survival
(HR = 1.40; p < 0.001)

Malcovati et al., Haematologica, 2006
Anemia – a key feature in MDS

- **Relevance of anemia**
  - Anemia affects vast majority of MDS patients (Anemia in ~90%; Hb < 10g/dL in ~50%; RBC-transfusions in ~80%)
  - Anemia results in an impaired quality of life (QoL)
  - Anemia & high transfusion frequency represent a risk factor for an unfavorable clinical course

- **Frequent RBC transfusions result in transfusion-related iron-overload**
  - After ~2o RBCs monitor iron overload based on serum-ferritin and eventually by MRI T2* (heart, liver) or echocardiography
  - Start iron chelation therapy based on international guidelines

CVD, cerebrovascular disease; DM, diabetes mellitus
Treatment options in anemic low-risk MDS (IPSS Low-grade / Int-I or IPSS-R very low, low, int-1)

Symptomatic anemia

Supportive therapy including transfusions & iron-chelation

- Del(5q)
  - Lenalidomid
    - ESA
  
  - EPO < 500 U/l and/or low transfusion need (<2U/month)  
    - ESA ± G-CSF

- EPO ≥ 500 U/l and/or high transfusion need  
  - Valproic-acid
  
  - Hypoplastic MDS
    - HLA-DR15  
      - CyA (ATG) 

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1 Licensed in this indication by EMA. Decreased response to Lenalidomid in TP53 mutated.
2 Based on predictive model (Nordic score). G-CSF might increase erythroid response to ESAs particularly in RARS.
3 Response more frequent in younger patients, in hypoplastic MDS and in HLADR-15.
4 5-Azacytidine might be effective in low risk MDS. However, EMA approval so far only for high-risk MDS and CMML. In contrast FDA-approval in low-risk MDS. Role in low-risk MDS is analysed in clinical studies.
5 Clinical studies in Non-5q low-risk MDS (RBC-TI ≥ 8 weeks in 26.9%) have been finished (Santini et al., #409, ASH 2014).
6 New drugs including TGFb superfamily ligand traps (Luspatercept) are in clinical studies.

ATG, anti-thymocyte globulin; CMML, Chronic myelomonocytic leukemia; ESA, erythro-poiesis-stimulating agent; CyA, Cyclosporin-A; RBC-TI, Red blood cells transfusion independent

Based on Stauder R. et al., 2008
Low-risk MDS (IPSS Low-grade / int-I or IPSS-R very low, low, int-1)
Assessment of Hb and iron status (TSAT, serum ferritin)

Hb <10 g/dL

- <2 RBC transfusions/month and/or serum EPO <500 IU/L
  - ESA*
  - no response after 8-12 weeks
    - 2nd line treatment†
  - Monitor Hb and iron status and maintain target levels with minimum treatment

- ≥2 RBC transfusions/month and serum EPO >500 IU/L
  - No del 5q
    - ESA*,‡
  - With del 5q
    - Lenalidomide

ESA-treated MDS patients who are iron-deficient and transfusion independent may be considered for i.v. iron treatment; † Second line anaemia treatment in MDS patients at low to intermediate risk can include anti-thymocyte globulin, hypomethylating agents and lenalidomide; ‡ this patient group reveals a low probability of response to ESA

TSAT Transferrin saturation, EPO erythropoietin

adapted from Fenaux et al., Ann Oncol, 2014 and Aapro et al., in preparation.
**ESA ± G-CSF in MDS**

Low-risk MDS displaying anemia ± transfusion need; Nordic Score at least +1
(Exclude hypocellular MDS and consider Lenalidomid in 5q- MDS)

**Non-RARS**

EPO 30,000 - 40,000U/w (or DAR 150mcg/w) ²,³

After 4-6 weeks No response ⁴

- Increase to 60,000/w or 300mcg/w
  - 8-12 weeks Response
  - 8-12 weeks No response

- Add G-CSF 300mcg/w ⁵
  - After 16 weeks No response - Halt

**RARS**

Epo 60,000 U/Woche (or DAR 300(150)mcg/w) + G-CSF 300mcg/w (100 3 days/week) 16 weeks ²,³,⁴,⁵

1 Refractory anemia with ring sideroblasts (RARS)
2 EPO (Erythropoietin alpha or beta), DAR (Darbepoietin)
3 Substitute iron depending on serum ferritin
4 Response might be defined by not achieving a minor erythroid response (IWG-criteria (Cheson, 2000): i.e. Hb increase of 1-2 g/dl in patients with pretreatment Hb <11 g/dl or at least a 50% reduction in transfusion requirement in transfusion-dependent patients. The target Hb is <120 g/l; when Hb >120 g/l stop; restart with 50% dose when Hb is < 120 g/l.
5 G-CSF: Aim to reach neutrophil count 6-9G/L.

Based on Stauder et al., 2008
Nordic Score to predict response to ESAs in MDS

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
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<tbody>
<tr>
<td>Transfusion RBC</td>
<td>&lt; 2U/month</td>
<td>≥ 2U/mo</td>
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<tr>
<td>Serum Epo*</td>
<td>&lt; 500 U/L</td>
<td>≥ 500 U/L</td>
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Probability of response: Total score 0: 74%; 1: 23%; 2: 7%

*Pretreatment values

Based on Hellström-Lindberg
Improved survival in ESA-treated MDS

- EPO plus G-CSF (n = 121) (Nordic phase II trials) vs untreated patients from Pavia, Italy (n = 237)
- EPO + G-CSF treatment associated with
  - Improved response rates: erythroid response rate was 39%, median response duration 23 months (range, 3 to 116+).
  - Better overall survival (hazard ratio, 0.61; 95% CI, 0.44 to 0.83; P = .002). This positive association was primarily observed in patients requiring fewer than 2 units of RBCs per month.
  - No association with the risk of acute myeloid leukemia (AML) evolution
- Conclusion: Treatment of anemia in MDS with EPO plus G-CSF may have a positive impact on outcome in patients with no or low transfusion need, while not affecting the risk of leukemic transformation.

Jädersten M. et al, JCO 2008
Recombinant erythropoietins in the EU

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<td></td>
<td></td>
<td>Binocrit(^a)</td>
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<tr>
<td></td>
<td>Epoetin beta</td>
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<td>Methoxy polyethylene glycol-epoetin beta</td>
<td>Mircera(^a)</td>
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CKD, chronic kidney disease; Cancer-related or chemotherapy-induced anemia (CRA, CIA); Myelodysplastic Syndromes (MDS)

\(^a\) Phase-3 studies in MDS are ongoing.
ESAs in MDS

- ESAs represent an effective treatment of anemia in low-risk MDS
  - Improve Hb levels, reduce transfusion need and increase QoL
  - ESAs have been used safely in larger numbers of MDS patients. No evidence for negative impact on survival or AML evolution in prospective (Greenberg et al.) or historical controls (Jadersteden et al., Park et al.)
  - ESAs even improve survival in treated patients (Jadersteden et al., Park et al.); however, no prospective, randomised study has demonstrated an OS benefit of ESA treatment. Two phase 3 clinical studies are ongoing to assess the efficacy of ESAs in MDS
  - Other causes of anemia like iron-, folate-, or B\textsubscript{12}-deficiency should be excluded
  - Responses within 8–12 weeks of treatment in 30-50%. Median response duration is \(~2\) yrs.
  - In general IPSS low- or int-1 risk, unilineage dysplasia (WHO) respond better than high-risk or multilineage dysplasia MDS \(\rightarrow\) exact diagnosis is essential
  - A predictive model exists (Nordic score) (Hellström-Lindberg et al.)
  - G-CSF might act synergistically with ESAs; MDS with ring sideroblasts (RARS) respond better to ESAs + G-CSF and should be treated upfront (Hellström-Lindberg et al.)
Thrombopenia in MDS

- Thrombopenia is common in MDS
  - <100 G/l in ~ 40–60%
  - <50 G/l in ~ 33%
  - <20 G/l in ~ 17%
  - Platelet transfusion dependent ~20%
- Due to hemorrhage frequent cause of morbidity & mortality
- Associated with decreased OS & higher AML-transformation
- Limits application of effective drugs like lenalidomide or azacitidine

Gonzalez-Porras JR et al., Cancer, 2011
Activity of TPO and TSAs

TPO, Thrombopoietin; TSAs, Thrombopoiesis stimulating agents; MPL, TPO-receptor

Charlotte K. Brierley & David P. Steensma, BJH, 2015
Thrombopoiesis stimulating agents (TSAs)

- Recombinant thrombopoietin (TPO); high immunogenicity limits clinical use
- Thrombopoiesis stimulating agents (TSAs); TPO-RA (TPO-receptor agonist)
  - Romiplostim (Nplate®)
  - Eltrombopag (Revolade®)
  - Others: avatrombopag, LGA-4665, NIP-004, butyzamide...
- Studies on TSAs mainly in chronic ITP
  - Reduction in bleeding events,
  - Side effects include VTE, bone marrow-fibrosis, development of neutralizing antibodies, hepatic dysfunction...
- Using Eltrombopag multi (tri-lineage) responses have been observed in some cases of aplastic anemia (stem cell cookie?) (Desmond R. et al., Blood, 2013)

ITP, immune thrombocytopenia; VTE, venous thromboembolism
TSAs registered so far by EMA

- **Eltrombopag (Revolade®)**
  - Small nonpeptide molecule; oral application
  - Is indicated (EMA) for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated. Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. Severe aplastic anemia (SAA) if insufficient response to immunosuppressive therapy (FDA).

- **Romiplostim (Nplate®)**
  - Peptibody; sc injection weekly
  - Is indicated (EMA) for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.
Treatment options in thrombopenic low-risk MDS (IPSS Low-grade or Int-1; IPSS-R very low, low, int-1)

Thrombopenia

Supportive therapy (platelet transfusions ¹)

Corticosteroid ²

Response

Be happy!

Insufficient response

TSAs ³

Azacitidine? ³

¹ Repeated platelet transfusions often induce allo-immunisation, thus rendering the patient refractory to further transfusions; ² Thrombopenia might be auto-immune mediated; ³ Not approved in this indication
MDS – Romiplostim relevant clinical studies

Phase 1/2 (Kantarjian H. et al., JCO, 2010; Sekeres et al., Cancer, 2011)
- Complete/major plt. response in 65%; transient elevations in BM-blast counts were observed, which reverted after drug stop

Phase 2 randomised (Giagounidis A. et al. Cancer, 2014)
- IPSS Low-risk/intermediate-1-risk MDS (N = 250) patients with thrombocytopenia were randomized 2:1 to receive romiplostim or placebo weekly for 58 weeks.
- The primary endpoint- the number of clinically significant bleeding events (CSBEs) per patient-had a hazard ratio for romiplostim:placebo of 0.83 (95% confidence interval, 0.66-1.05; P = .13).
- An independent data monitoring committee advised halting study drug because of concerns regarding excess blasts and AML rates with romiplostim (interim hazard ratio, 2.51). At 58 weeks, the AML rates were 6% in the romiplostim group and 4.9% in the placebo group (hazard ratio, 1.20; 95% confidence interval, 0.38-3.84), and the overall survival rates were similar.
- Romiplostim treatment in patients with low-risk/in-1-risk MDS increased platelet counts and decreased the number of bleeding events and platelet transfusions. Although study drug was discontinued because of an initial concern of AML risk, survival and AML rates were similar with romiplostim and placebo.

Concomitant therapy in myelosuppressive therapy (in combination with azacitidine, decitabine or lenalidomide)
Based on clinical data from phase 2 study a predictive scoring model was developed. Parameters are endogenous thrombopoietin (THPO) levels and number of prior platelet transfusions. For thrombocytopenic patients with lower-risk MDS, lower baseline THPO levels (<500 pg/ml) and limited platelet transfusion history predicted a greater likelihood of a subsequent platelet response to romiplostim.

Sekeres A et al. BJH, 2014
MDS – Eltrombopag relevant clinical studies

MONOTHERAPY

Two global, randomized, placebo-controlled studies are ongoing in MDS / AML
Phase I/II (MDS/AML)– PMA112509 ; Phase II (MDS/AML) TRC114968

A phase II, multicentre, placebo-controlled, single blind study of eltrombopag in low/intermediate-1 risk MDS with platelet count <30 G/l is ongoing (EQoLMDS).

- Planned enrolment 171 patients randomized 2:1 to placebo.
- Eltrombopag is being administered at dose ranges of 50–300 mg
- Interim analysis for 21 patients (eltrombopag) and 10 patients (placebo) 12 of 15 in the treatment cohort achieved a platelet response, with significant improvement in fatigue and measures of quality of life. No increase in BM blasts has been observed with eltrombopag (Oliva et al, EHA, 2013).

CONCOMITANT THERAPY

Phase II Dose-Escalation of Eltrombopag in Patients Receiving Azacitidine for MDS/AML (Dickinson MJ et al., #4657 ASH 2014)

- Platelet improvement in 54% (13/24) of patients with baseline platelets <100 at median (range).
- Eltrombopag could be safely delivered at these doses.

A randomized, double-blind, placebo-controlled, phase III, multi-centre study of eltrombopag or placebo in combination with azacitidine in IPSS int-1, int-2 and high-risk MDS (SUPPORT) is ongoing
MDS and TSAs - Conclusions

- TSAs are promising in MDS as monotherapy as well as concomitant therapy
  - Improvement in platelet counts
  - Reduction in bleeding
  - Reduction of need for transfusions

- However, interpretation of data is difficult
  - Trial cohorts have been relatively small, thus confounding interpretation
  - Moreover the outcome data are influenced by bias
  - MDS represents a heterogeneous disease and patients are heterogeneous too

- Rising blast counts / potential to AML-transformation remain a concern
- TSAs cannot yet be routinely recommended in MDS.
- Clinical studies are ongoing.
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