Myelodysplastic Syndromes: Update in Diagnosis and Therapy

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MDS: Typical Features

- Dysplasia in one or more Cell Lineages in the BM
- Peripheral Cytopenia (unilineage, bi-, or pan-CP)
- Quality of Anemia (macrocytic, Tf-dependent, ..)
- Prominent Erythropoiesis in the BM

MDS: Classification

- FAB (RA, RARS, RAEB, RAEB-T, CMML) until 2001
- WHO (REAB-T & CMML deleted, new: 5q-, RC MD)
- Updated WHO Classification 2008
Risk Assessment in MDS

Age, ECOG, Co-Morbidity
de novo vs secondary
Duration (previous blood pictures)
Subtype (FAB, WHO)
Single prognostic variables
(blasts, cytopenias, karyotype)

Scoring systems* → IPSS / WPSS
→ LDH-adjusted IPSS

*TWO ENDPOINTS: a) survival b) AML
Therapy of MDS: Major Goals

• Antineoplastic Therapy
  - Eradication of the clone – CR, CCR
  - Cytoreduction (palliative treatment)

• Supportive Therapy
  - Quality of Life (QOL)
  - Prevention & Therapy of Iron Overload
  - Management of Consequences of Cytopenia
Intensive Therapy in MDS

- Stem Cell Transplantation (SCT)
- Polychemotherapy (CT) - similar as for high risk AML

i) In a group of pts: Consider poly-CT prior to SCT
ii) SCT as appropriate consolidation after CT (CR)
iii) CT without SCT → high risk of relapse

WHEN SCT (TIMING) ?
IPSS LOW (INT-1): wait until progression occurs !
IPSS INT-2/HIGH: consider immediate CT+SCT !
→ maximum survival
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Notes</th>
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<tr>
<td><strong>Decitabine</strong> (5-aza-2-deoxycytidine)</td>
<td>no CT or SCT</td>
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<td><strong>Acazytidine</strong> (5-azacytidine; Vidaza®)</td>
<td>possible (at least 3 cycles before response evaluation)</td>
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<td><strong>Lenalidomide</strong> (Revlimid®)</td>
<td>5q- patients</td>
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<td><strong>ATG + CSA</strong></td>
<td>young pts, low risk, RA, HLADR15! (hypoplastic) (PNH subclone)</td>
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Die Daten der Studie: **Efficacy of Lenalidomide in Myelodysplastic Syndromes**
List et.al entnehmen sie bitte
http://content.nejm.org/cgi/content/full/352/6/549

**Myelodysplastic Syndromes — Coping with Ineffective Hematopoiesis**
Mario Cazzola, M.D., and Luca Malcovati, M.D. finden Sie unter
http://content.nejm.org/cgi/content/extract/352/6/536
Erythropoietin in MDS

- Only a Subgroup of Patients are Responders (sometimes transient response)
- Scoring can predict Response to EPO
- In some patients, additional G-CSF may be required to achieve good responses (RARS)

Predictive Variables:
- Frequency of Transfusions
- Endogenous EPO (<100 U/L; <500 U/L)
- MDS Subtype (e.g. RARS)
before starting EPO:

- Diagnosis by FAB / WHO criteria
- Determination of risk category (IPSS, WPSS)
- Treatment plan (curative intervention ?)

- Evaluation of Transfusion-Dependence
  (observation for several weeks !)
- Measurement of endogenous EPO level
- Scoring (to predict probability of response)
Comparative Meta-Analysis of Erythroid Response Rates for EPO and Darbepoetin in MDS

Meta-analysis was performed to compare erythroid response rates defined as major plus minor response of the 2 erythropoiesis-stimulating agents currently available for the treatment of anemia.

9 Epoetin alfa studies with total of 619 patients
Patients evaluable for erythroid response rate = 589

8 Darbepoetin alfa studies with a total of 442 patients
Patients evaluable for erythroid response rate = 389

Therapy with EPO: Proposed Algorithm*

- Start with EPO (in RARS + G-CSF ?) in Tf-dependent
- Observe for approximately 6-8 weeks
- In responders → continue with EPO
- In non-responders → consider G-CSF
  as an attempt (1-2 mcg/kg/d; 2-3 x/w)
  or increase EPO dose
- Observe for several weeks
- In responders → continue EPO (+G-CSF)
  and decrease dose to tolerance & effect
- In non-responders → stop cytokines
  and initiate alternative therapy

* adapted from NCCN guidelines
• Do we need iron chelation therapy for patients with MDS?

• Which patients with MDS may benefit from iron chelation?
Iron-chelating Agents - Indications for patients with MDS (ÖGHO)

- Iron Overload (serum ferritin >2000) and
- Erythrocyte Transfusions and
- Life expectancy > 2 years!

- Frequent Erythrocyte Transfusions (>2 per months) and
- Life expectancy > 2 years!

- Life expectancy < 2 years + special situation: e.g. planned curative therapy; Fe-induced organ damage,

Iron-chelating Agents

- Desferoxamine (Desferal®) s.c. (i.v.)
- Deferiprone (Ferriprox®) p.o. (neutropenia)
- Deferasirox (Exjade®) p.o.
  cave: renal function!
Treatment with Ferriprox®
(Desferripron, Deferipron, L1)

• bidentate iron chelator
• three molecules of L1 binding one atom of iron
• more lipid soluble → rapid gastrointestinal absorption → access to intracellular iron pools
• excreted via the urine

- Most serious side effect: **Severe agranulocytosis (~ 0.5%)**
  (mild neutropenia ~ 8.5%)
  → regular monitoring of neutrophil count required

• Under debate:
  - long-term efficacy?
  - progression of liver fibrosis?

• Licensed by the EMEA but not by the FDA
ICL670 (Exjade) in MDS:

- One year of ICL670 treatment suggests a dose-dependent effect on LIC levels in this population of MDS patients.
- There was also a trend towards a dose-dependent effect on serum ferritin levels, despite the known variability in this parameter.
- This study therefore appears to confirm the utility of serum ferritin as a marker for the efficacy of iron chelation therapy.
- ICL670 treatment was generally well tolerated. The most common drug-related AEs were mild, transient gastrointestinal AEs, which are similar to the AEs reported with other oral iron chelation therapies.
- Once-daily, oral iron chelation therapy with ICL670 appears to be effective and well tolerated for the treatment of iron overload in patients with MDS.
Iron-chelating Agents - Standard

- Desferal – still standard first line!

- In pts who cannot tolerate Desferal or have no adequate response → Exjade*

- Response Evaluation: serum ferritin, etc

  * cave: Creatinin, Creatinin-clearance
Exjade bei MDS: Praktisches Vorgehen und Empfehlungen

- Evaluieren: 1) FAB, WHO, IPSS, 2) Ery-Tf-Frequenz, 3) alle therapeutischen Optionen ausgeschöpft, 4) Survival-Estimate

- Start-Dosis: 10-20 mg/kg/Tag – vor allem bei bereits erhöhtem Serum Kreatinin cave! ZIEL: 30 mg/kg/Tag; Kreatinin-Clearance vor Start Therapie, und dann 1/Woche in den ersten 3 Wochen. Danach Serum-Kreatinin alle 1-3 Wochen (falls alle Werte stabil)

- Dosismodifikation: 30 mg/kg/Tag falls kein Ansprechen in geringerer Dosierung; bei steigendem Krea – Dosisreduktion möglich – Dosis konstant <20 mg/kg/Tag wenig sinnvoll!