TRANSFUSIENOOD EN PROGNOSE BIJ MDS

W.V.T.V. 20 Apr 2012

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Diagnosis of MDS
MDS comprises a heterogeneous group of clonal haematopoietic stem-cell malignancies

- MDS is characterised by
  - BM dysplasia\(^1,2\)
    - hypercellular BM is present in 90% of cases
    - hypocellular BM is present in ~10% of cases
  - ineffective haematopoiesis
  - peripheral cytopenias
  - a risk of progression to AML and death

AML = acute myeloid leukaemia
BM = bone marrow

Age-related Incidence of MDS

Age-specific incidence rates (per 100,000)

- Less than 50: 0.5
- 50-59: 5.3
- 60-69: 15
- 70-79: 49
- 80 and over: 89

Causes of death in MDS

Leukemia

Others

Bleeding/infection
Classification of MDS
### WHO system: categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>BM blasts, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>RA with unilineage erythroid dysplasia</td>
<td>&lt;5</td>
</tr>
<tr>
<td>RARS</td>
<td>RA with unilineage erythroid dysplasia and ringed sideroblasts (&gt;15%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>RCMD</td>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>&lt;5</td>
</tr>
<tr>
<td>RCMD-RS</td>
<td>RCMD and ringed sideroblasts (&gt;15%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>Subgroup of RAEB; &lt;5% blasts in blood; no Auer rods</td>
<td>5–9</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>Subgroup of RAEB; 5–19% blasts in blood; patients with Auer rods</td>
<td>10–19</td>
</tr>
<tr>
<td>MDS del(5q)</td>
<td>MDS with isolated deletion of chromosome 5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>MDS unclassifiable</td>
<td>MDS-U; cannot be classified in above categories</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

- With the WHO system, patients with ≥20% BM blasts are diagnosed as having AML

WHO system: OS based on a retrospective analysis of 467 patients with MDS

Prognosis of MDS: IPSS
# IPSS: risk classification

<table>
<thead>
<tr>
<th>Score value</th>
<th>BM blasts (%)</th>
<th>Karyotype</th>
<th>Cytopenias</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5</td>
<td>Good (normal, –Y, del[5q], 20q–)</td>
<td>0–1</td>
</tr>
<tr>
<td>0.5</td>
<td>5–10</td>
<td>Intermediate (other)</td>
<td>2–3</td>
</tr>
<tr>
<td>1.0</td>
<td>–</td>
<td>Poor (complex or chromosome 7)</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>11–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>21–30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Int-1</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
</tr>
</tbody>
</table>

IPSS: OS based on a retrospective analysis of 816 patients with MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Median OS, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>Int-1</td>
<td>3.5</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.2</td>
</tr>
<tr>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Prognosis of MDS: WPSS
WPSS: introduction

• The WPSS incorporates additional variables that affect prognosis and are not included in the IPSS\(^1\)
  – transfusion dependency
  – karyotype
  – WHO category

• Provides dynamic prognostic information throughout a patient’s clinical course\(^2\)

# WPSS: risk classification

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>RA, RARS, del(5q)</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>–</td>
</tr>
<tr>
<td>Transfusion</td>
<td>No</td>
<td>Regular</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3–4</td>
</tr>
<tr>
<td>Very high</td>
<td>5–6</td>
</tr>
</tbody>
</table>

WPSS: distribution of risk groups in a retrospective study of 739 patients with MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>74</td>
</tr>
<tr>
<td>Low</td>
<td>162</td>
</tr>
<tr>
<td>Intermediate</td>
<td>170</td>
</tr>
<tr>
<td>High</td>
<td>244</td>
</tr>
<tr>
<td>Very high</td>
<td>89</td>
</tr>
</tbody>
</table>

WPSS: OS based on retrospective study of 426 patients with MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>103</td>
</tr>
<tr>
<td>Low</td>
<td>72</td>
</tr>
<tr>
<td>Int</td>
<td>40</td>
</tr>
<tr>
<td>High</td>
<td>21</td>
</tr>
<tr>
<td>Very high</td>
<td>12</td>
</tr>
</tbody>
</table>

Summary and conclusions

• Accurate classification and evaluation of prognosis is difficult due to the heterogeneous nature of MDS, essential to facilitate selection and timing of appropriate treatment.

• Two classification systems for MDS are used widely:
  – FAB – defines five subtypes of MDS
  – WHO – uses a more refined BM classification to define eight subtypes of MDS

• Two commonly used systems have been developed to improve prognostic evaluation:
  – IPSS assesses prognosis at diagnosis only
  – WPSS provides a more subjective classification and can be used throughout the duration of the disease

• WHO-based classification and prognostic evaluation may ultimately provide the most useful guide to selection of appropriate treatment for optimal outcomes.
MDS: Treatment Options

- Best supportive care, including iron chelation
- Hematopoietic growth factors
- Immunosuppressive treatment
- Differentiation induction
- Farnesyltransferase inhibitors
- Thalidomide / Revlimid
- Arsenic trioxide
- Low-dose chemotherapy
- Epigenetic treatment
- Intensive chemotherapy
- Allogeneic stem cell transplantation
~ 80% of MDS patients have a hemoglobin <10 g/dl at diagnosis*, the majority become transfusion-dependent.

* Sanz GF et al., Blood 74:395-408, 1989
In most patients with MDS symptomatic anaemia is managed with blood transfusions.

RBC-TD has many disadvantages:
- Iron overload associated with hepatic, pituitary, pancreatic and cardiac dysfunction
- Potential for infection
- Volume overload
- Acute/delayed reactions
- Possible immunosuppression
- Alloimmunisation
- Expensive
- Inconvenient

The role of RBC transfusions in patients with MDS:
- According to NCCN guidelines RBC transfusions should be used as an adjunct to treatment for symptomatic anaemia.

Many patients with MDS become RBC-TD:
- Up to 90% of patients with MDS will receive transfusions.
- Many (~39–79%) will become RBC-TD.

References:
1. NCCN Guidelines on Myelodysplastic Syndromes V.2.2011
In RBC-TD patients, repeated transfusions may not prevent periods of severe symptomatic anaemia

Hb levels in a RBC-TD multiple myeloma patient not receiving any other treatment for anaemia

Hb = haemoglobin

Impact of anaemia and RBC-TD on survival and disease progression in patients with MDS
RBC-TD has a negative impact on survival in patients with MDS independently from IPSS

LFS = leukaemia-free survival

In patients with MDS the severity of RBC-TD correlates with survival

**OS**
(HR=1.36; p<0.001)

**LFS**
(HR=1.40; p<0.001)

Malcovati L, et al. Haematologica 2006;91:1588–90
Chronic anaemia is associated with an increased risk of non-leukaemic death (NLD)

A retrospective analysis of 920 MDS patients from a single centre in Pavia, Italy (mean age [range] = 67.5 years [18–93])

Rates of NLD in males (n=558)
Rates of NLD in females (n=362)

Impact of iron overload in patients with MDS
RBC-TD can lead to iron overload in patients with MDS

- The average adult can only store ~7g total body iron
- 1U of RBC contains ~200–250 mg of iron
- The body has no physiologic mechanism for secreting iron
- Patients who are transfused with 4 RBC units per month will accumulate ~9.6g of iron per year which exceeds storage capacity
- Patients can become overloaded with iron after ~20 transfusions

List A. Cancer Control 2010;17 (Suppl 1):1–8
Iron overload has an additional impact on survival in RBC-TD patients with MDS

Impact of anaemia and RBC-TD on HRQoL in patients with MDS
RBC-TD has a negative impact on HRQoL in patients with MDS

Cross-sectional study performed in 39 consecutive MDS patients. HRQoL was assessed using QOL-E\textsuperscript{©}; patients stratified by RBC-TD

Impact of anaemia and RBC-TD on comorbidities in patients with MDS
Comorbidities are very common in patients with MDS (>50% of patients)

Retrospective analysis of 840 MDS patients diagnosed 1992–2007 (Pavia Group)

Prevalence, %

Cardiac 25
Cerebrovascular 5
Mild-moderate pulmonary 3
Severe pulmonary 2
Mild hepatic 14
Moderate-severe hepatic 3
Renal 4
Solid tumour 10
Diabetes 11

Cardiac problems are the most prevalent comorbidity in patients with MDS

Assessing the impact of comorbidities on outcome in patients with MDS: survival and risk of NLD

Impact of MDS-CI on OS and NLD based on retrospective analysis of 840 MDS patients diagnosed between 1992–2007 (Pavia Group)

MDS-CI is more likely to deteriorate over the course of disease in RBC-TD versus RBC-TI patients

Impact of RBC-TD on the deterioration of comorbidities based on retrospective analysis of 840 MDS patients diagnosed between 1992–2007 (Pavia Group)

In patients with clinically relevant comorbidities, particularly cardiac disease, treatment of symptomatic anaemia is mandatory in order to limit further deterioration of those comorbidities

Impact of anaemia and RBC-TD on comorbidities in patients with MDS: focus on cardiac function
The main cause of NLD in patients with MDS is cardiac failure.

Retrospective analysis of 840 MDS patients diagnosed 1992–2007 (Pavia Group)

Cases, %

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>63</td>
</tr>
<tr>
<td>Infection</td>
<td>23</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>7</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>4</td>
</tr>
</tbody>
</table>
Severe anaemia is associated with increased risk of cardiac death

A retrospective analysis of 920 MDS with MDS from a single centre in Pavia, Italy

Probability of cardiac death according to the presence of severe anaemia (Hb <9 g/dL for males and Hb <8 g/dL for females)

HR = 8.1; p<0.004

Pathophysiology of anaemia: impact on cardiac function

Non-haemodynamic and haemodynamic mechanisms compensate for anaemia

- Lower affinity of oxygen for Hb
- Increased erythropoeitin production

- Increased cardiac output due to enhanced LV contractility
- Vasodilation
- Lower blood viscosity
- Increased heart rate

May lead to cardiac remodelling: histopathological and structural changes that lead to a progressive decline in LV performance

LV = left ventricular

Cardiac mortality in patients with MDS may be related to iron overload

In a retrospective analysis of 292 patients with RBC-TD MDS or AA, patients who died from cardiac or liver failure had received significantly more transfusions than those who died from other causes.

- 97% of patients who died from cardiac or hepatic failure had iron overload (serum ferritin ≥1,000µg/L)

AA = aplastic anaemia

Burden of chronic anaemia in patients with MDS: summary

- Anaemia is a major clinical problem in patients with MDS
  - ~80% patients are anaemic at diagnosis

- In patients with MDS, anaemia has a negative impact on
  - survival
  - risk of non-leukaemic death
  - HRQoL

- In patients with MDS, the severity of anaemia correlates with
  - blast count
  - IPSS category

Burden of transfusion dependency in patients with MDS: summary

- In most patients with MDS, chronic anaemia is managed with blood transfusions\(^1\)
  - many (~40–80%) patients become transfusion dependent\(^2\)
- Transfusion dependency can lead to iron overload\(^3\)
- In patients with MDS, transfusion dependency has a negative impact on
  - survival\(^4\)
  - progression to AML\(^4\)
  - HRQoL\(^5\)
  - prevalence of comorbidities\(^6\)
  - deterioration of comorbidities over the course of the disease\(^7\)
  - healthcare costs\(^8\)
- Achievement of transfusion independence is a major goal of the clinical management of patients with MDS

Aantallen Bloedgroep antigenen en ABO en Rh allelen

Daniels et al, ISBT 2007a
1. Transfusie-afhankelijke patiënten met hemoglobinoopathie dienen zo vroeg mogelijk getypeerd te worden voor de bloedgroepen van het Rhesus, Kell, Duffy, Kidd en MNS systeem, waarbij de zeer zeldzame S- en s-negatieve patiënten ook uitgetypeerd moeten worden voor bloedgroep U.


en MDS ?
Predisposition:

**Acquired:**

- Senescence
- Mutagen/Genotoxic Stress
  - Therapeutic alkylators, Topo-II agents, β-emitters (\(^{32}\)P), autoSCT
  - Environmental/occupational (benzene)
  - Tobacco
- Aplastic anemia
- PNH

**Heritable:**

- Constitutional genetic disorders
  - Trisomy 8 mosaicism
  - Familial monosomy 7
  - Neurofibromatosis 1
  - Embryonal dysgenesis (del12p)
- Congenital Neutropenia
  - Kostmann, Schwachman-Diamond
- DNA repair deficiencies
  - Fanconi anemia, AT, Bloom syndrome
- Pharmacogenomic polymorphisms
  - (GSTq1-null)

How does RBC-TD impact on patients’ HRQoL? Statements based on MDS patient forum discussions

- Requires a significant amount of time to be spent at a health care facility
- Requires the availability and accessibility of health care facilities
- Perception that life is arranged around medical appointments
- Leads to fatigue and tiredness that limit performance of routine physical activities
- Interferes with social functioning and family life
- May lead to anxiety about the future
- May lead to moderate/severe discomfort
- May lead to anxiety regarding risk of infections
- Reliance on family, or other caregiver support, to take care of oneself and to undertake routine activities
- Perception that one is a burden to family due to health condition
- Feeling of sadness, hopelessness, and helplessness because of health condition