Management of low and high risk MDS

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Brussels, 4th October 2014
Low / int 1 risk MDS

Improve QOL
Improve cytopenia

Int 2 / high risk MDS

Delay progression To AML

Improve Survival

AlloSCT

Intensive chemotherapy

Hypomethylating agents

Low dose AraC

Supportive care

EPO

ATG, CsA

Lenalidomide

TPO receptor agonists

Oral iron chelators

Low / int 1 risk MDS

Treatment intensity
Treatment of low/int 1 risk MDS
Transfusion dependence and iron load in MDS

- 1 U of RBC contains ~200–250 mg iron
- Patients who are transfused with 2 RBC units per month will receive ~ 5–6g iron per year
- The body has no physiological mechanism for removal of excess iron
- Patients can become overloaded with iron after 20-40 transfusions
Probability of non-leukaemic death in low risk MDS according to transfusion dependency

Malcovati, JCO, 2005, 23: 7594
Exjade = Deferasirox

- Eliminates iron by faecal route; binds free iron in plasma
- **Intake**
  - Once daily 30 minutes before meal
  - Tablets dispersed in water or orange juice
- **Start dose** 20 mg/kg, dose modification depending on ferritin
- **Side effects**:
  - Gastrointestinal
  - Skin rash
  - Renal failure, generally mild
- **Discontinuation rate in EPIC study (MDS)**: 49 % at 1 year
- **Indication**:
  - low/int risk MDS +
    high transfusion need and /or high ferritin (> 2000 ng/ml)
  - candidates for alloSCT
Iron chelation in patients with low-risk MDS: impact on survival

170 transfusion dependent MDS patients included during a 1 month period in 2005, *prospectively* followed and reanalyzed 2 yrs later

TELESTO study of deferasirox in MDS patients: study design

- **Prospective, randomized**, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in 630 MDS patients

- **Primary study end-point**: event-free survival (death, cardiac and hepatic non-fatal events)

Deferasirox 10 mg/kg/day (first 2 weeks); then 20 mg/kg/day  n = 420

Placebo  n = 210

Screening (1 month)  Randomization (2:1 = deferasirox:placebo)

1 year  2 years  3 years  4 years  5 years

How to select patients for EPO treatment?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
<th>Score</th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion requirement*</td>
<td>&lt;2 U/month</td>
<td>0</td>
<td>≥2 U/month</td>
<td>1</td>
</tr>
<tr>
<td>Serum EPO*</td>
<td>&lt;500 U/L</td>
<td>0</td>
<td>≥500 U/L</td>
<td>1</td>
</tr>
</tbody>
</table>

*Pretherapeutic levels

Predicted response

Score = 0: 74%
Score = 1: 23%
Score = 2: 7%

# EPO ± G-CSF in low/int1-risk MDS: OS and AML transformation

<table>
<thead>
<tr>
<th></th>
<th>EPO ± G-CSF</th>
<th>No EPO ± G-CSF</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>French-EPO</td>
<td>IPSS/IMRAW</td>
<td></td>
</tr>
<tr>
<td>cohort (n=284)</td>
<td></td>
<td>cohort (n=225)</td>
<td></td>
</tr>
<tr>
<td>5-year OS</td>
<td>64%</td>
<td>39%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-year AML</td>
<td>12%</td>
<td>13%</td>
<td>0.21</td>
</tr>
<tr>
<td>transformation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IMRAW = International MDS Risk Analysis Workshop**

ESA are safe and efficient
but are not registered or reimbursed for low risk MDS
MDS low risk : thrombocytopenia

Randomized study comparing placebo and romiplostim in low/int1 risk MDS with low platelet count

*Giagounidis, ASH 2011, Cancer 2014*

- Survival identical in both arms
- Romiplostim arm
  - Improvement of platelet count
  - Reduction of bleeding events
  - Reduction of platelet transfusions
  - Interim analysis: more progression to AML (2.4% vs 6.0%); study prematurely stopped
  - AML risk not confirmed in later analysis
Deletion 5q is the most common chromosomal abnormality found in MDS patients. Deletion 5q (15%) includes isolated del(5q), Del(5q) plus one additional abnormality, and complex abnormalities†. 5q-syndrome (5%) encompasses (Primary) MDS with 30–50% chromosomal abnormalities. *Based on study of 2124 MDS patients; includes del(5q) ± additional abnormalities. †Del(5q) + two additional abnormalities. Haase D et al. Blood. 2005;106:232a [abstract 787]
MDS-003: Lenalidomide in patients with del(5q) 
MDS improves erythropoiesis

Transfusion independent 67%
Major Cytogenetic response 45%

Median duration of TI: 2.2 years

*As of 12/4/06. Symbols in line graph are censored patients who remained TI at time of data cutoff or at time of study discontinuation.

List AF, et al. 
Presentation at ASH 2006. Abstract 251
MDS-004: significant improvements in RBC-Transfusion independency in patients randomized to lenalidomide versus placebo.

* *p<0.001 versus placebo
Bars represent 95% CI
mITT population

Best erytroid and cytogenetic responses are obtained with Lenalidomide 10 mg starting dose without increased toxicity

Combined analysis of MDS-003 and MDS-004: impact of Cytogenetic Response on clinical outcomes

Analysis included a total of 286 lenalidomide-treated patients with del(5q) MDS

Achievement of CyR was associated with significantly longer OS

Risk of AML progression appeared to be higher in patients without CyR

Lenalidomide alters natural evolution of 5q-MDS

Log-rank p=0.0517

Log-rank p<0.0001

CyR = cytogenetic response

MDS-004: does LEN increase risk of AML?

The placebo group includes 56 patients (84%) who had not achieved at least minor response by week 16 and were, therefore, crossed over to LEN 5 mg.

3 yr AML risk = 25%

Cross over at 6 months

Log-rank $P = 0.3657$

The placebo group includes 56 patients (84%) who had not achieved at least minor response by week 16 and were, therefore, crossed over to LEN 5 mg.

• Transfusion-dependent anaemia
• Due to low- or intermediate-1-risk MDS
• Associated with an *isolated* deletion 5q at cytogenetic analysis
• When other therapeutic options are insufficient or inadequate
• EU registration trial: MDS-004
## Results of lenalidomide in low / int-1 risk MDS

<table>
<thead>
<tr>
<th></th>
<th>MDS 003 (5q-)</th>
<th>MDS 002 (non 5q-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>148</td>
<td>214</td>
</tr>
<tr>
<td>Transfusion independence</td>
<td>67 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Total erythroid response</td>
<td>76 %</td>
<td>43 %</td>
</tr>
<tr>
<td>Major Cytogenetic response</td>
<td>45 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Time to TI</td>
<td>4.6 weeks</td>
<td>4.8 weeks</td>
</tr>
<tr>
<td>Hgb rise</td>
<td>+ 5.4 g/dl</td>
<td>+ 3.2 g/dl</td>
</tr>
<tr>
<td>Duration of TI</td>
<td>2.2 years</td>
<td>41 weeks</td>
</tr>
<tr>
<td>Mode of action of lenalidomide</td>
<td>Selective toxicity against 5q – clone</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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**Mode of action of lenalidomide**

- **Selective toxicity against 5q – clone**
- **Unknown**
MDS-005 (Celgene) : phase III

MDS Low/Int 1 risk

Non 5 q (-)

Transfusion dependent and EPO resistant

1:2

Placebo

Lenalidomide
10 mg / day

Primary endpoint: proportion of pts becoming transfusion independent
European consensus guidelines for low risk MDS

European consensus guidelines for INT-1 MDS
Treatment of int2 /high risk MDS
Low / int 1 risk MDS
Improve QOL
Improve cytopenia

Int 2 / high risk MDS
Delay progression To AML
Improve Survival

Supportive care

EPO
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Oral iron chelators

Lenalidomide
TPO receptor agonists

Low dose AraC
Hypomethylating agents
Intensive chemotherapy
AlloSCT

Treatment intensity
Long-term disease-free survival in higher risk MDS patients treated with intensive chemotherapy is poor.

Survival (% patients)
100
90
80
70
60
50
40
30
20
10
0
0             24           48
72            96
120          144

Months

Duration of CR (n=280)
CR rate at 5 years = 16%
Overall survival (n=510)
Survival rate at 5 years = 8%

Age < 60 or normal karyotype: better 5 yrs OS

CR 50-60 %, high relapse rate, high treatment related mortality

Low-dose AraC in patients with AML or high-risk MDS (AML14)

Based on a trial comparing LDAC versus HU in 217 patients with AML or high-risk MDS (> 10% blasts), low-dose AraC may be an option in patients deemed unfit for intensive chemotherapy.

Complete remission rate

Survival

No difference in poor karotypes

LDAC = low-dose Ara-C; ATRA = all-trans retinoic acid
HU = hydroxyurea

DNA hypermethylation is reversible

**Normal**

**Hypomethylating agents**

**DNA methyl transferase**

**Cancer**

MDS

Expressed

Silencing of regulatory genes (e.g. tumor suppressor genes)

Courtesy of Issa, JP
Hypomethylating Cytosine Analogs

- Cytosine
- 5-methyl-cytosine
- 5-aza-cytidine (azacitidine)
- 5-aza-2’-deoxycytidine (decitabine)
- Vidaza (Celgene)
- Dacogen (J&J)

Vidaza and Dacogen are FDA/EMA approved for MDS.
AZA-001: phase III survival study

Treatment continued until relapse, unacceptable adverse events, disease progression

Randomization

MDS Int2-High (n = 358)

Investigator selection of Conventional Care Regimens

AZA 75 mg/m²/day SC for 7 days every 28 days (n = 179)

Conventional care regimens (n = 179)
- Best supportive care only
- Low-dose cytarabine (20 mg/m²/day for 14 days every 28–42 days)
- Standard chemotherapy (7 + 3)

AZA provides significant clinical benefits

**ORR (CR+PR)**

- AZA: 29% (n = 179)
- CCR: 12% (n = 179)

*P = 0.0001*

**HI (major + minor)**

- AZA: 49% (n = 179)
- CCR: 29% (n = 179)

*P < 0.0001*

*Evaluated by investigator; †Evaluated according to IWG criteria.

CR, complete response; HI, hematologic improvement; IWG, International Working Group; ORR, overall response rate; PR, partial response.

AZA-001: time to progression to AML

Time to AML progression (months)

HR=0.5
p<0.0001

Azacitidine 17.8
CCR 11.5

AZA is the only hypomethylating agent that significantly prolongs OS and is first line therapy in high risk MDS.

Difference in median OS was 9.5 months.

Log rank $P < 0.0001$
AZA-001: overall survival across prespecified subgroups

<table>
<thead>
<tr>
<th>ITT subgroup</th>
<th>Favours azacitidine</th>
<th>Favours CCR</th>
<th>Total event/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td></td>
<td></td>
<td>195/358</td>
</tr>
<tr>
<td>Age: ≥65 (RAEB &amp; RAEB-T)</td>
<td>$&lt;65$</td>
<td>$≥65$</td>
<td>$≥75$</td>
</tr>
<tr>
<td>FAB: RAEB</td>
<td>RAEB-t</td>
<td></td>
<td>95/207</td>
</tr>
<tr>
<td>WHO: RAEB-1</td>
<td>RAEB-2</td>
<td></td>
<td>15/31</td>
</tr>
<tr>
<td>Cytogenetics: Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>80/167</td>
</tr>
<tr>
<td>Karyotype: –7/del(7q)</td>
<td></td>
<td></td>
<td>42/57</td>
</tr>
</tbody>
</table>

AZA-001: OS in AML (20–30% BM blasts)

The graph shows the proportion of patients surviving over time from randomization in months. The orange line represents AZA, and the blue line represents CCR.

Key points:
- **AZA** significantly prolonged OS compared with CCR.
- **AZA** had a median survival of 24.5 months, compared to 16.0 months for CCR.
- **50.2%** of AZA patients were alive at 24.5 months, compared to **15.9%** of CCR patients at 16.0 months.
- Log rank $P = 0.005$
- HR 0.47; 95% CI 0.28–0.79
- Deaths: AZA = 24; CCR = 41

**References**
AZA-001: OS in patients who achieved HI as best response

List AF, et al. Oral presentation at ASCO 2008, Chicago, IL, USA
Continued AZA treatment increases probability of response

Median time to first response is 2 cycles

Range: 1–22 cycles

AZA incorporation into DNA requires actively dividing cells

- Serial cycles of DNA replication needed
- Hypomethylation occurs gradually
- Extensive demethylation requires multiple exposures to the drug

Vidaza: Practical issues

• Unstable after reconstitution
  – Storage at room t°: < 45 min
  – Storage at 2-8 °C: < 8 hours
  – Reconstitution with cool water: < 22 hours

• Common side effects
  – Myelosuppression and Infections
  – Nausea, vomiting
  – Diarrhea and constipation
  – Mucositis
  – Local skin reactions
Vidaza EU Label 2008

• Vidaza is indicated for:
  – **Int-2 / High-risk** MDS (IPSS)
  – CMML with 10–29% marrow blasts without MPD
  – WHO-classified **AML** with 20–30% blasts and multilineage dysplasia
  – not eligible for HSCT
Randomized phase III EORTC-German MDS Study group trial

High/Int2 MDS
> 60 yr
Not eligible for intensive therapy

Decitabine IV
15 mg/m2 x 9
Over 3 days

Supportive care

Primary endpoint: overall survival
**Decitabine vs BSC in Int/High-Risk MDS**

**OS**

- **Median OS, Mos**:
  - Decitabine: 10.1
  - BSC: 8.5

- **OS (%)**

- **Pts at Risk, n**
  - BSC: 71, 38, 22, 10, 6
  - Decitabine: 83, 53, 24, 15, 4

- **HR: 0.88 (95% CI: 0.66-1.17; log-rank P = .38)**

**PFS**

- **Progression-Free Survival (%)**

- **Pts at Risk, n**
  - BSC: 33, 15, 7, 3, 1
  - Decitabine: 62, 32, 11, 2, 0

- **Log-rank test**
  - $P = .004$

Decitabine

- DNA
  - DNA hypomethylation
  - Cell cycle arrest
  - Differentiation

Azacitidine

- RNA
  - Inhibits methylation of Ribosomal RNA or Transfer RNA
  - Inhibits protein synthesis
  - Cytotoxicity
Future options for hypomethylating agents in MDS

- **Prolonged treatment schedules**
  - Vidaza: 10 days SC (30 % trilineage responses)

- **New indications**
  - Lower risk MDS
  - after alloTx: maintenance, relapse

- **New formulations**: oral Vidaza

- **Combinations**:
  - Lenalidomide
  - HDAC inhibitors (Vorinostat)
Phase I: Oral vidaza in Low-INT1 MDS with transfusion dependency or platelet count \(\leq 50,000\) (Garcia –Manero ASH 2012)

RBC transfusion independence responses

- **14d: 7 cycles (range: 2-15) (n=26)**
  - 53.5%
  - 8/15 sustained for 56 days (8 weeks)
  - 6/15 sustained for 84 days (12 weeks)

- **21d: 5 cycles (range: 1-17) (n=27)**
  - 46.7%
  - 14/30 sustained for 56 days (8 weeks)
  - 3/15 sustained for 84 days (12 weeks)

- **Total (N=53)**
  - 33.3%
  - 20/60 sustained for 56 days (8 weeks)
  - 5/30 sustained for 84 days (12 weeks)

- **Total (N=53)**
  - 26.7%
  - 8/30 sustained for 84 days (12 weeks)
AZA-MDS-003: study design

- Phase III, multicentre, randomised, double-blind, placebo-controlled study

**Patient characteristics (n=386)**
- IPSS low- or inter-1-risk MDS
- RBC transfusion dependent
- and Platelets \( \leq 50,000/\mu L \)

**Stratification Randomisation 1:1**

**At end of cycle 6**
- Responders continued double-blind treatment
- Non-responders discontinue double-blind treatment

**Azacitidine, orally 300 mg /day 21 days in cycles of 28 days**

**Placebo 21/28 days**

**Primary endpoint:** RBC-TI for \( \geq 12 \) weeks

**Secondary endpoints:** Overall survival, HI(E/P), AML progression, PLT-TI, bleeding events

**Belgian centres:** UZ Leuven, Brugge, Charleroi, KLINA
Combination study
Lenalidomide + Vidaza

• Sekeres, Blood 2012, phase I + II

5AZA 75 mg/m² x 5 days SC + LEN 10 mg x 21/28 days PO

HR – MDS  n = 36

no 5q-

ORR  72 %

CR  44 % (> AZA monotherapy)

CR duration  > 17 mths

well tolerated

randomized study planned
Open Chromatin
Transcriptionally Active

Condensed Chromatin
Transcriptionally Inactive

Acetylated Histone tails

Deacetylated Histone tails

HDAC inhibitors

Histone Deacetylase (HDAC)
A Phase II Trial Of Vorinostat In Combination With Azacitidine In high risk MDS

Lewis R. Silverman, ASH 2013

Table 1.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No</th>
<th>Aza mg/m2 Subcutaneous (SC)</th>
<th>Days (aza)</th>
<th>Vorinostat mg daily PO</th>
<th>Days (Vorinostat)</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>55</td>
<td>1-7</td>
<td>400</td>
<td>3-16</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>75</td>
<td>1-7</td>
<td>600</td>
<td>3-9</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>55</td>
<td>1-7</td>
<td>400</td>
<td>3-9</td>
<td>67</td>
</tr>
</tbody>
</table>
SWOG-S1117: North American Intergroup Randomized Phase II MDS/CMML Trial

Groups: SWOG, ECOG, CALGB, NCIC

Total sample size: 240
Primary objective: 20% improvement of RR based on 2006 IWG Criteria
Secondary objectives: OS, RFS, LFS
Power 81%, alpha 0.05 for each combo arm vs AZA
Anticipated time: 2.5 yrs

Higher-risk MDS (IPSS > 1.5 or blasts > 5%)

- AZA (n = 80)
- AZA + Lenalidomide (n = 80)
- AZA + Vorinostat (n = 80)

Clinicaltrials.gov. NCT01522976
Is there life after vidaza failure?

Survival analysis in GFM and AZA001 according to the salvage treatment regimens.

Prébet T et al. JCO 2011;29:3322-3327
MDS and allo-SCT

- AlloSCT is only curative option for MDS
- High *relapse rate* in advanced MDS
- Myeloablative allo SCT:
  - Was limited to 5-10 % of MDS patients
  - High *treatment-related mortality* up to 30 %
- Reduced intensity alloSCT
  - Up to 70 yrs
RIC versus standard conditioning in MDS: A retrospective study of EBMT

RIC Allogeneic HCT in Older Patients With de Novo MDS: optimal timing

IPSS Low/Intermediate-1 Risk

- Nontransplantation therapy
- RIC transplantation

IPSS Intermediate-2/High Risk

- Nontransplantation therapy
- RIC transplantation

Can Vidaza replace allo-SCT?
Allo SCT versus AZA in MDS: a matched comparison

HR MDS, sec AML > 5% blasts
Age 60-70 yrs old

Allo cohort: German MDS SG, FHRCC
Aza cohort: French MDS group
No donor available or unfit for alloSCT

Platzbecker, BBMT, sept 2012
AZA versus allo SCT?

- Randomized study ongoing in Germany

HR-MDS 55-70 yrs old

4 x AZA, donor search

continue AZA

if no donor

allo SCT

if donor
European consensus guidelines for INT2-High risk MDS

Still a long way to go ….

Life Expectancy in MDS

- Higher-risk MDS treated with supportive care
- Higher-risk MDS treated with azacitidine
- IPSS low-risk MDS
- Healthy man
- Healthy woman

US Department of Health and Human Services data.
CHALLENGES AHEAD