Poročilo EHA 2012

Simon Bitežnik
Burden of chronic anaemia in patients with MDS

- Anaemia is a major clinical problem in patients with MDS
  - ~80% patients are anaemic at diagnosis\(^1\)
- In patients with MDS, anaemia has a negative impact on
  - Survival\(^2\)
  - Risk of NLD\(^2\)
  - HRQoL\(^3\)
- In patients with MDS, the severity of anaemia correlates with IPSS category\(^4\)

EPO therapy may improve OS in erythroid responders

Treated with EPO (n=403)
Untreated (n=628)

*from diagnosis or from EPO treatment initiation

Park et al. Blood 2008;111:574–82
Not all MDS patients will respond to EPO: prognostic factors

At multivariate analysis, factors associated with response were:

- Transfusion-independence
- Serum EPO levels
- Karyotype
- Baseline Hb levels

For each g/dl increase in pre-treatment Hb, the probability of response increased by 98% (p=0.02)

Univariate Cox regression analysis of response

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% confidence internal)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.011 (0.981–1.042)</td>
<td>0.464</td>
</tr>
<tr>
<td>Males</td>
<td>0.792 (0.385–1.628)</td>
<td>0.526</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>0.995 (0.980–1.010)</td>
<td>0.507</td>
</tr>
<tr>
<td>Serum Epo levels</td>
<td>0.993 (0.986–1.000)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hb</td>
<td>1.845 (1.235–2.756)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>0.479 (0.244–0.938)</td>
<td>0.032</td>
</tr>
<tr>
<td>LDH</td>
<td>1.000 (0.999–1.002)</td>
<td>0.720</td>
</tr>
<tr>
<td>Ferritin</td>
<td>1.000 (1.000–1.000)</td>
<td>0.845</td>
</tr>
<tr>
<td>TD</td>
<td>2.867 (1.354–6.070)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Poor response to EPO in patients with del(5q) versus non-del(5q) MDS

Retrospective analysis of 345 patients with MDS treated with EPO or DAR

Response rate:
- del(5q) n=48: 48%
- non-del(5q) n=297: 64%

Response duration:
- del(5q) n=48: 14 months
- non-del(5q) n=297: 25 months

DAR = darbepoietin

MDS-004: significant improvements in RBC-TI in patients randomised to lenalidomide versus placebo


†mITT population defined as patients with centrally confirmed MDS who received ≥1 dose

**RBC-TI (%)**

- Placebo (n=51)
- LEN 5mg (n=47)
- LEN 10mg (n=41)

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

Protocol defined (≥26 weeks)

IWG 2000 (≥8 weeks)
Lenalidomide vs placebo
Erythroid response associated with better survival

Azacitidine induces erythroid responses in higher risk MDS

<table>
<thead>
<tr>
<th>Response</th>
<th>AZA</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responses (CR + PR)</td>
<td>23 (23%)*</td>
<td>0%</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>7 (7%)†</td>
<td>0%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>16 (16%)†</td>
<td>0%</td>
</tr>
<tr>
<td>Haematological improvement</td>
<td>37 (37%)</td>
<td>5%</td>
</tr>
</tbody>
</table>

*P<0.0001; †P<0.01

BSC = Best supportive care

Patients experiencing haematological improvement with azacitidine treatment have a better OS

List AF, et al. Oral presentation at ASCO 2008; Chicago, IL, USA

Survival

Time from randomisation

p≤0.0001
HR=0.23 [95% CI: 0.10–0.51]
Conclusions

• Iron chelation therapy in MDS patients receiving transfusions may be associated with a better outcome

• Treatment with ESAs in lower-risk MDS induces erythroid responses in 40–70% of cases
  • Responders experience improvements in QoL and a better survival

• Lenalidomide in lower-risk MDS with del(5q) induces erythroid responses and cytogenetic changes
  • Responders experience improvements in QoL and a better survival

• Patients with higher-risk MDS receiving azacitididine may experience erythroid responses
  • Responders experience improvements in QoL and a better survival
Cytogenetic abnormalities are very common in patients with MDS

- 52% of patients had clonal abnormalities; 44% of these patients had >1 abnormality
- The most common abnormality was del(5q)

Analysis of a database of 2,124 patients with MDS

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Cytogenetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
<td>del(5q)</td>
</tr>
<tr>
<td>300</td>
<td>-7/del(7q)</td>
</tr>
<tr>
<td>250</td>
<td>trisomy(8)</td>
</tr>
<tr>
<td>200</td>
<td>del(20q)</td>
</tr>
<tr>
<td>150</td>
<td>-5</td>
</tr>
<tr>
<td>100</td>
<td>-17/del(17p)</td>
</tr>
<tr>
<td>50</td>
<td>trisomy(21)</td>
</tr>
<tr>
<td>50</td>
<td>inv(3q)</td>
</tr>
<tr>
<td>20</td>
<td>-13/del(13q)</td>
</tr>
<tr>
<td>20</td>
<td>-21</td>
</tr>
<tr>
<td>5</td>
<td>t(5q)</td>
</tr>
<tr>
<td>5</td>
<td>trisomy(11)</td>
</tr>
<tr>
<td>5</td>
<td>del(12p)</td>
</tr>
<tr>
<td>5</td>
<td>del(11q)</td>
</tr>
<tr>
<td>5</td>
<td>t(7q)</td>
</tr>
<tr>
<td>5</td>
<td>+Mar</td>
</tr>
</tbody>
</table>

MDS = myelodysplastic syndrome

Del(5q) MDS is not 5q– syndrome

- All MDS
- MDS with chromosomal aberrations
- del(5q) MDS
  - WHO MDS with isolated del(5q)
  - del(5q) + 1 additional abnormality
  - complex abnormalities*

- OS = 4.8–68.4 months
- OS = 7–80 months
- OS = 24 months
- OS = 66 months
- OS = 107 months

*del(5q) with ≥2 additional abnormalities
OS = overall survival

Additional risk factors in patients with del(5q) MDS: further chromosomal abnormalities

Retrospective analysis of 541 del(5q) MDS patients assessed in the pre-lenalidomide era

- Two distinct risk groups: isolated del(5q) and del(5q)+1; del(5q) + ≥2
- Three distinct risk groups: isolated del(5q); del(5q) + 1; del(5q) + ≥2

Additional chromosomal abnormalities are associated with reduced survival

Additional chromosomal abnormalities are associated with increased AML transformation

Additional risk factors in patients with del(5q) MDS: BM blast percentage

Retrospective analysis of 60 patients with isolated del(5q) MDS; median follow-up = 53 months

- del(5q) with <5% BM blasts
- del(5q) with ≥5% BM blasts

Cumulative survival

Time (months)

p=0.00005

BM = bone marrow

Combined analysis of MDS-003 and MDS-004: impact of karyotypic complexity on clinical outcomes

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

Karyotype complexity had a negative impact on OS

Karyotype complexity had a negative impact on AML progression

Median OS

- Isolated del(5q)
- del(5q) + 1
- del(5q) + ≥2

Probability of survival

- 3.9 years
- 3.0 years
- 1.8 years

Log-rank p=0.0016

Probability of AML progression

- Log-rank p=0.0044

AML = acute myeloid leukaemia

**TP53 mutations in MDS and their impact on patient outcomes**

Retrospective analysis of the incidence and prognostic impact of *TP53* mutations in patients with del(5q) using next-generation sequencing

Patient characteristics (n=318)

- Median age, years (range): 65 (17–72)
- IPSS risk, n (%)
  - low: 71 (24)
  - int-1: 101 (32)
  - int-2: 58 (18)
  - high: 29 (9)
- 40 patients (12%) received BM transplant, IC, azacitidine or lenalidomide

*TP53* mutational status

- Patients with mutation, n (%): 30 (9.4)
- Median clone size, % (range): 42 (2.5–93)

**OS by TP53 mutational status***

<table>
<thead>
<tr>
<th>Mutational Status</th>
<th>All patients</th>
<th>Isolated del(5q)</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>NR (&gt;66)</td>
<td>66</td>
<td>14.1</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>9.7</td>
<td>23</td>
<td>9.6</td>
</tr>
</tbody>
</table>

**p<0.0001**

**p<0.002**

**p<0.0001**

*TP53 mutations are an independent prognostic marker in patients with MDS and del(5q)*

Multivariate analysis †: TP53 mutational status was the strongest predictor for OS and PFS (p<0.0001 for both)

*Survival analysis was censored at treatment date

†Co-variables: age, sex, WHO subtype, IPSS risk, ±mutations; progression-free survival

Commonly retained regions versus commonly deleted regions in del(5q) MDS

Analysis of 1,155 MDS/MPN/AML patients to characterise 5q disorders and identify the impact of associated genomic lesions, by SNP-A and MC.

Del(5q) frequency

- MDS (n=473)
- MDS/MPN (n=62)
- AML (n=252)

5q lesions

- MC
- SNP-A

Additional abnormalities

MC = metaphase cytogenetics
SNP-A = single-nucleotide polymorphism array
UPD = uniparental disomy

Diagnosis of del(5q) MDS: methodology

- Standard MC is integral to the diagnosis of del(5q) MDS
- Guidelines stipulate that ≥25 metaphases should be analysed

- Fluorescence in situ hybridisation (FISH)
  - May play a supplementary role to standard MC especially when insufficient metaphases are available
  - FISH detected del(5q) in 6% of 637 MDS patients who had normal karyotype by MC at diagnosis

- SNP array (SNP-A) karyotyping
  - SNP-A can detect microdeletions and regions of UPD that are undetectable by MC or FISH
  - Can improve detection of del(5q) in conjunction with MC and FISH

UPD: uniparental disomy
SNP: single-nucleotide polymorphism

Technological advances: FISH for improving diagnosis of primary MDS

Patients and methods

- 121 patients with suspected primary MDS
- Conventional cytogenetic analysis of BM samples
  - informative karyotype (≥20 metaphases obtained) for 90 patients
- Samples from remaining 31 patients analysed by FISH

Conventional cytogenetics

- Normal: 37%
- Del(5q): 27%
- Trisomy 8: 7%
- -7/7q-: 9%
- Other*: 20%

FISH

- Normal: 70%
- Del(5q): 5%
- Trisomy 8: 6%
- -7/7q-: 18%
- Other*: 6%

* hypo/hyperdiploid karyotype, complex karyotype, unusual deletions and/or translocations

FISH and del(5q)

Study design

Screening (n=716)
BM analysis by MC

Group A
5q– not detected by MC (n=637)

Group B
5q– detected by MC (n=79)

FISH detected del(5q) in 38/637 (6%) cases in which MC had not identified 5q–

Authors’ recommendation:
FISH may help in classification of cases with
- Suspected 5q– syndrome
- No metaphases or metaphases are not evaluable
- Abnormal karyotype without evidence of 5q–

SNP arrays can detect additional ‘cryptic’ abnormalities

Increased detection of cytogenetic abnormalities

N=430

\[ p<0.0001 \]

Novel lesions were detected with SNP in:

- 54\% of normal/non-informative conventional karyotyping results
- 62\% of abnormal conventional karyotyping results

Newly detected lesions by SNP-A indicated a poorer patient prognosis

MC and SNP-A analyses of 5q disorders: impact of lesions on prognosis

Loss of additional genes in the distal regions of 5q may contribute to a poorer prognosis in patients with del(5q) abnormalities

OS

PFS

PFS = progression-free survival

Considerations with cytogenetic techniques

Metaphase cytogenetics only → Complement with FISH?

FISH is limited by the probes used; it is too expensive to use probes against entire genome → FISH must complement, not replace, metaphase cytogenetics

SNP-A is much more sensitive than FISH, but it can miss chromosomal translocations → If SNP-A becomes routinely used, it should be in conjunction with other techniques
FISH on enriched CD34+ PB cells to monitor genetic response to lenalidomide: LE-MON-5 study

Preliminary cytogenetic findings in 37 patients with lower-risk WHO-defined MDS and isolated del(5q) treated with lenalidomide

<table>
<thead>
<tr>
<th>Study start</th>
<th>Every 2–3 months</th>
<th>Every 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotyping and FISH on BM aspirates</td>
<td>FISH on enriched CD34+ PB cells</td>
<td>Karyotyping and FISH on BM aspirates</td>
</tr>
</tbody>
</table>

Fast responders (n=14)*
>50% clone size reduction in ≤2 months†

Slow responders (n=14)*
>50% clone size reduction in >2 months†

Non-responders (n=9)*
No cytogenetic response detected

FISH analysis of CD34+ PB cells, in combination with standard MK, could be a powerful non-invasive tool to monitor response to lenalidomide therapy

*Based on time to cytogenetic remission
†Each line represents one patient

Summary and conclusions

- Del(5q) is the most common cytogenetic abnormality in patients with MDS\(^1\)
- Some patients with isolated del(5q) MDS have distinct features: ‘5q– syndrome’\(^2\)
- Del(5q) MDS is highly heterogeneous: a number of factors have a negative impact on prognosis, e.g.\(^3\)
  - Transfusion dependence
  - Elevated blast count
  - Additional genomic aberrations
  - Thrombocytopenia
  - Age >65 years
- Technological advances, e.g. FISH analysis on PB CD34+ cells and SNP arrays, will facilitate the monitoring of disease evolution and response to therapy in individual patients\(^4,5\)
- When considering treatment options, clinicians need to assess the risk profile of individual patients

Possible link between mechanism of action of lenalidomide and observed clinical data

RBC-TD patient with lower-risk del(5q) MDS: severe anaemia; no other cytopenias

Lenalidomide

Targeted apoptosis of abnormal clone

Replacement of del(5q) precursors by normal ones

Initial worsening of cytopenias

High probability of cytogenetic remission

Reduced probability of progression to AML

Pro-erythroid effect on normal cells

Increased normal erythropoiesis

Reduced RBC-transfusion requirement

Achievement of RBC-TI

Reduced probability of non-leukaemic death

Within days?

Cycle 1–2

Median time to RBC-TI: 4.6 weeks

Median time to CyR: 8 weeks

>1 year

**MDS-003 and MDS-004 study design**

**Patient characteristics**
- IPSS low-/int-1-risk MDS
- Del(5q) ± additional abnormalities
- RBC transfusion dependent
- ANC >500 cells/µL
- Platelets >25,000/µL*

**MDS-003**
- (n=148)
- Lenalidomide
  - 10mg/day
  - 21/28-day cycles
  - For 24 weeks

**MDS-004**
- (n=205)
- Lenalidomide
  - 10mg/day
  - 28-day cycles

- OR
  - Lenalidomide
    - 5mg/day
    - 28-day cycles
  - OR
  - Placebo

**Primary endpoint:**
- erythroid response†
- RBC-TI (for ≥56 consecutive days)

**Secondary endpoints:**
- RBC-TI duration
- cytogenetic response
- tolerability

**References**

---

†As defined by the IWG 2000 criteria
‡Double-blind phase; at 16 weeks, responders continued double-blind treatment for 1 year, non-responders entered open-label treatment or withdrew
* MDS-003: >50,000/µL
Achievement of CyR was associated with significantly longer OS

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

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

CyR = cytogenetic response

MDS-004: OS and progression to AML in patients who achieved RBC-TI

In patients treated with lenalidomide, achievement of RBC-TI for ≥8 weeks was associated with improved OS and reduced risk of AML progression

*Landmark 6-month analysis

Combined analysis of MDS-003 and MDS-004: impact of karyotypic complexity on clinical outcomes

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

Karyotype complexity had a negative impact on OS

Karyotype complexity had a negative impact on AML progression

Median OS
- Isolated del(5q): 3.9 years
- del(5q) + 1: 3.0 years
- del(5q) + ≥2: 1.8 years

p<0.01 for del(5q) + ≥2 vs. Isolated del(5q)

Log-rank test: p=0.0016 for Isolated del(5q) vs. del(5q) + ≥2

Probability of AML progression

Log-rank test: p=0.0044 for del(5q) + ≥2 vs. del(5q) + 1

Combined analysis of MDS-003 and MDS-004: predictive factors for progression to AML

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate analysis p-value</th>
<th>Multivariate analysis Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion burden, units/8 weeks</td>
<td>&lt;0.001</td>
<td>1.13 (1.06–1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>del(5q) ≥2 vs isolated del(5q)</td>
<td>&lt;0.001</td>
<td>3.97 (1.89–8.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBC-TI ≥26 weeks (no vs yes)</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Patients with del(5q) MDS and ≥2 additional cytogenetic abnormalities were at ~97% increased risk of progression to AML than patients with isolated del(5q) MDS

Objective: to retrospectively compare AML progression and OS in lenalidomide-treated vs untreated RBC-TD patients with lower-risk del(5q) MDS

Patients were selected from clinical trials and registries

MDS-003
n=148

MDS-004
n=205

Multicentre registry*
n=459

Eligibility criteria for present study:
• IPSS low- or int-1 risk MDS with del(5q)
• RBC-TD (≥1 unit/8 weeks)
• ANC ≥500/μL
• Platelets ≥50,000/μL

Lenalidomide-treated patients
n=295
Median follow-up: 4.3 years (range 0.02–6.8)

Untreated patients
n=125
Median follow-up: 4.6 years (range 0.06–19.4)

*Nine centres of MDS registries in Europe, USA, Australia

Comparative study of AML progression and OS with lenalidomide therapy: baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Lenalidomide treated</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Median RBC transfusions, units/8 weeks</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>BM blasts 5–10%, %</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Median Hb, g/dL</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Cytogenetics, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>isolated del(5q)</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>del(5q) +1 abn</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>del(5q) + &gt;1 abn</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>IPSS risk, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low-1</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>int-1</td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

*Nine centres of MDS registries in Europe, USA, Australia

Comparative study of AML progression and OS with lenalidomide therapy: OS

Comparative study of AML progression and OS with lenalidomide therapy: progression to AML

Cumulative incidence of AML progression

Median time to AML progression: not reached

Number of patients at risk

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Untreated</th>
<th>LEN-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>125</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>79</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>128</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>98</td>
</tr>
</tbody>
</table>

Comparative study of AML progression and OS with lenalidomide therapy: predictive factors

Predictive factors for AML progression and OS

Relative hazard (multivariate Cox proportional hazard model)

**Decreased**

- LEN-treated vs untreated
- IPSS risk (int-1 vs low)
- Transfusion burden, units/8 weeks

**Increased**

- LEN-treated vs untreated
- IPSS risk (int-1 vs low)
- Transfusion burden, units/8 weeks
- Age, years
- Gender (female vs male)

Hazard ratio (95% CI)

- **Decreased**
  - p=0.741
- **Increased**
  - p=0.041
  - p=0.017
  - p=0.003*
  - p=0.002
  - p<0.001
  - p=0.003

Treated patients showed improved survival
Lenalidomide was not associated with increased risk of AML progression

*Only significant when using multivariate Cox proportional hazard model

Summary and conclusions in patients with del(5q) MDS

- Lenalidomide induces durable erythroid responses; ~65% achieved RBC-TI
- Lenalidomide treated and untreated patients showed no difference in the risk of AML
- Possible risk factors for progression for treated and untreated patients included
  - Increased medullary blast count
  - Complex karyotype
  - Transfusion need
  - No response to treatment (CyR/ RBC-TI)
  - P53 mutation?
- Advice:
  - Response assessment at ~4 months, end of treatment in case of non-response
Intensive chemotherapy (IC) in patients with int-2/high-risk MDS: low survival rate

- CR rate 55%
- Induction mortality 17%

n=510; Median age 63 years

OS after 5 years 8%

Survival with palliative treatment of high-risk MDS and AML in patients aged >60 years not fit for IC

- An analysis of 36 studies (median age: 70 years)\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-intensity therapies</td>
<td>12</td>
</tr>
<tr>
<td>BSC alone</td>
<td>7.5</td>
</tr>
</tbody>
</table>

- Median survival was 4 months in a randomised study (low-dose cytarabine [LDAC] vs hydroxyurea)\(^2\)

<table>
<thead>
<tr>
<th>No. patients</th>
<th>No. events</th>
<th>Obs. – Exp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD Ara-C</td>
<td>103</td>
<td>100</td>
</tr>
<tr>
<td>HU</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

\(p=0.0009\)

How can survival be improved in elderly patients with high-risk MDS and AML?

1. Effective consolidation therapy [ex. haemopoietic stem cell transplant (HSCT) including RIC-HSCT]

In 613 centres in 42 countries
RIC = reduced-intensity conditioning

Outcome at 5 years after RIC-HCT in MDS and AML

Median follow-up 42 months (n=256), median age 62 years

OS (%)

OS = 40%

DFS (%)

DFS = 35%

RI (%)

RI = 48%

NRM (%)

NRM = 27%

Azacitidine prolongs overall survival in patients with IPSS Int-2 or High-risk MDS

<table>
<thead>
<tr>
<th>Cytogenetic risk group</th>
<th>Patients, % (n/N)</th>
<th>Median OS, months</th>
<th>Aza</th>
<th>CCR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>47 (167/358)</td>
<td>Not reached</td>
<td></td>
<td>17.1</td>
<td>0.59</td>
</tr>
<tr>
<td>Intermediate</td>
<td>21 (76/358)</td>
<td>26.3</td>
<td></td>
<td>17.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Poor</td>
<td>28 (100/358)</td>
<td>17.2</td>
<td></td>
<td>6.0</td>
<td>0.53</td>
</tr>
</tbody>
</table>

CCR = conventional care regimen

Only CR has a favorable impact on survival with chemotherapy in MDS and AML

IC in MDS\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>252</td>
<td>192</td>
</tr>
<tr>
<td>Other</td>
<td>154</td>
<td>135</td>
</tr>
</tbody>
</table>

\(p<0.0001\)

\[\text{Median survival of 66 days in non-remitters vs 575 days in patients with CR (overall CR rate of 18\%)}^2\]

AML 14 non-intensive – overall survival

Favourable/intermediate

<table>
<thead>
<tr>
<th></th>
<th>Percentage still alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD Ara-C</td>
<td>100</td>
</tr>
<tr>
<td>HU</td>
<td>100</td>
</tr>
</tbody>
</table>

\(p=0.004\)

AML 14 non-intensive – overall survival

Adverse

<table>
<thead>
<tr>
<th></th>
<th>Percentage still alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD Ara-C</td>
<td>100</td>
</tr>
<tr>
<td>HU</td>
<td>100</td>
</tr>
</tbody>
</table>

\(p=0.4\)

AZA-001: response in elderly patients with 20–30% blasts*

The CR rate was similar in the AZA and CCR groups, suggesting that AZA-mediated improvement in OS occurred independently of response.

*WHO-defined AML
AZA-001: OS by best response

OS by best response (IWG, 2000)

2-year survival rates

- HI (p<0.0001)
- PR (p=0.006)
- CR
- CCR

Patients surviving (%)

Time from randomisation (months)

Adapted from List AF, et al. Oral presentation at ASCO 2008, Chicago, IL, USA
Adverse cytogenetics has a strong negative impact on survival after chemotherapy in MDS and AML

Survival according to cytogenetics

- Normal
- Abnormal, non-complex
- Complex

After IC

p = 0.0001

AML 14 non-intensive – overall survival

After LDAC

- Favourable/intermediate
- Adverse

No CR with LDAC in adverse cytogenetics!!

AZA 001: AZA vs LDAC in patients with IPSS Int-2- or High-risk MDS regarding cytogenetics

<table>
<thead>
<tr>
<th></th>
<th>AZA</th>
<th>LD Ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>Median number of cycles</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Median OS</td>
<td>24.5</td>
<td>15.3</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS good-risk cytogenetics</td>
<td>NR</td>
<td>19</td>
</tr>
<tr>
<td>HR=0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS poor-risk cytogenetics</td>
<td>24.5</td>
<td>2.9</td>
</tr>
<tr>
<td>HR=0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>31%</td>
<td>12%</td>
</tr>
<tr>
<td>p=0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>53%</td>
<td>25%</td>
</tr>
<tr>
<td>p=0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion independent</td>
<td>45%</td>
<td>13%</td>
</tr>
<tr>
<td>p=0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe infections/patient-year</td>
<td>0.44</td>
<td>1</td>
</tr>
<tr>
<td>p=0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days in hospital/patient-year</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Old age is not a contraindication to treatment with AZA

AZA-001 sub-group analysis ≥75 years of age

HR: 0.48 (95% CI: 0.26–0.89); p=0.0193

No. at Risk
AZA   38   31   27   14   9   3   0   0   0   0
CCR   49   37   23   16   5   3   1   0   0   0

Azacitidine in patients with AML

Azacitidine prolongs overall survival in elderly patients with 20–30% blasts*

*p = 0.004

Patients surviving (%)

Time since randomisation (months)

Azacitidine (n=55)
CCR (n=58)

50.2%
24.5 months
16.0 months


*WHO-defined AML
AZA-001: analysis of patients with 20–30% blasts (WHO AML) – infections and hospitalisation

Rates of infection requiring i.v. antibiotics

- AZA: 0.6 (rate per patient year)
- CCR: 1.1 (rate per patient year)

Rates of hospitalisation

- AZA: 3.4 (rate per patient year)
- CCR: 4.3 (rate per patient year)

Number of days in hospital

- AZA: 26 (days per patient year)
- CCR: 51 (days per patient year)

OSHO trial: AZA in patients with newly diagnosed or relapsed/refractory AML

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=40)</th>
<th>Newly diagnosed (n=20)</th>
<th>Relapsed or refractory (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>72</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (48)</td>
<td>11 (55)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Median BM blasts, %</td>
<td>42</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Median WBC count × 10⁹/L</td>
<td>3.6</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Cytogenetics,† n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>28 (70)</td>
<td>15 (75)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>High risk</td>
<td>12 (30)</td>
<td>5 (25)</td>
<td>7 (35)</td>
</tr>
</tbody>
</table>

- AZA 75 mg/m²/day subcutaneously for 5 days every 4 weeks
- Median follow-up duration was 13 months (range: 9–16 months)
AZA improves survival in AML patients with HI or better and newly diagnosed patients have longer OS

Median OS for patients with SD was 4 months, whereas median OS for patients with CR, PR, or HI was not reached (p=0.045); (median bone marrow blasts 42%)

AZA in elderly AML patients unfit for IC

- n=98
  - Median age: 76 years
  - WBC >10 g/L: 14 (14.2%)
  - Median BM blasts, %: 35 (20–85)
  - Cytogenetic risk, n (%):
    - Favourable: 0
    - Intermediate: 48 (48.9)
    - Adverse: 44 (44.8)

**AZA**
- 75 mg/m²/day x 7 days, 28-day cycles
  - median 6 (1–27) cycles

**ORR (CR + CRi + PR + HI) = 51%**

**Toxicity**
- 60 (61.2%) patients required hospitalisation for infections
- Death rate in first 2 months: 17%
  - from AML progression: 83%
  - from infections: 17%

AZA in elderly AML patients unfit for IC

**OS (n=98)**

- 1-year OS: 50%
- 2-year OS: 28%

**OS by cytogenetics (n=92)**

- Intermediate vs Adverse, p=0.005

**OS by patient characteristics: multivariate analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status (≥2 vs &lt;2)</td>
<td>0.98 (0.49–1.96)</td>
<td>0.96*</td>
</tr>
<tr>
<td>LDH (&gt;normal vs ≤normal)</td>
<td>1.98 (1.02–3.88)</td>
<td>0.045</td>
</tr>
<tr>
<td>Cytogenetics (adverse vs intermediate)</td>
<td>2.38 (1.29–4.41)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

AZA appears to be a valuable option for AML patients considered unfit for CT

AZA versus IC or BSC in 182 elderly WHO-AML patients

Retrospective study of AZA compared with IC or BSC on OS in patients >60 years old

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>AZA† (n=67)</th>
<th>IC (n=47)</th>
<th>BSC† (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>71 (60–84)</td>
<td>65 (60–75)</td>
<td>76 (62–89)</td>
<td>0.04, &lt;0.01*</td>
</tr>
<tr>
<td>Median leucocyte count, ×10⁹/L (range)</td>
<td>4.4 (0.2–17.5)</td>
<td>28.6 (0.8–166)</td>
<td>17.6 (0.4–211)</td>
<td>0.01, &lt;0.01*</td>
</tr>
<tr>
<td>Median BM blasts count, % (range)</td>
<td>34 (20–84)</td>
<td>64 (24–93)</td>
<td>47 (21–90)</td>
<td>0.003, &lt;0.01*</td>
</tr>
<tr>
<td>ECOG ≥2, n (%)</td>
<td>45 (67)</td>
<td>7 (15)</td>
<td>60 (88)</td>
<td>&lt;0.01, &lt;0.01*</td>
</tr>
<tr>
<td>Cytogenetics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>46 (68.6)</td>
<td>32 (68)</td>
<td>39 (57.3)</td>
<td>0.86*</td>
</tr>
<tr>
<td>Adverse</td>
<td>15 (22.3)</td>
<td>12 (25.5)</td>
<td>12 (17.6)</td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>6</td>
<td>3</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

AZA group:
- AZA 75–100 mg/m²/day s.c. (7 days of 28-day cycle)
- Median cycles: 6 (1–24)
- Median follow-up: 7.4 (1–28.3) months

IC group:
- Cytarabine 100–200 mg/m²/day c.i.v. (7 days)
- + Idarubicin 9–12 mg/m²/day (3 days)
- + HSCT
- Median follow-up: 13 (2–46) months

BSC group:
- Oral CT agents
- Transfusions
- Antibiotics with G-CSF
- Median follow-up: 5 (0–10) months

*IC vs AZA groups; †patients not eligible for IC

AZA versus IC or BSC in 182 elderly WHO-AML patients: outcomes

Significantly better survival with AZA was associated with: CR, PR or HI (p=0.018)

ORR = 38%

Patients (%)

1-year OS

2-year OS

In elderly patients with AML not eligible for IC, AZA led to an OS comparable to the one observed in patients treated with IC

# AZA & allogeneic HSCT in MDS and AML

## Prior to HSCT

Retrospective analysis: 417 patients receiving allogeneic HSCT between 1999 and 2009

<table>
<thead>
<tr>
<th>Characteristics at diagnosis, per pre-HSCT therapy</th>
<th>BSC (n=171)</th>
<th>AZA (n=49)</th>
<th>Induction CT (n=180)</th>
<th>AZA + induction CT (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS, n (%) Low/Int-1</td>
<td>108 (64)</td>
<td>16 (33)</td>
<td>73 (42)</td>
<td>7 (41)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IPSS, n (%) Int-2/High</td>
<td>60 (36)</td>
<td>32 (67)</td>
<td>102 (58)</td>
<td>10 (59)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics at transplantation, per pre-HSCT therapy</th>
<th>BSC (n=171)</th>
<th>AZA (n=49)</th>
<th>Induction CT (n=180)</th>
<th>AZA + induction CT (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>51 (44–57)</td>
<td>60 (30–62)</td>
<td>56 (18–61)</td>
<td>58 (32–61)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Disease progression, n (%)</td>
<td>32 (19)</td>
<td>7 (15)</td>
<td>95 (53)</td>
<td>10 (59)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BM blasts &lt;5%, n (%)</td>
<td>77 (52)</td>
<td>33 (67)</td>
<td>131 (74)</td>
<td>9 (53)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>–</td>
<td>33 (69)</td>
<td>131 (73)</td>
<td>9 (53)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

AZA & allogeneic HSCT in MDS and AML
Prior to HSCT: OS and NRM by treatment

3-year OS per prior treatment
- AZA
- Induction CT
- AZA + induction CT

3-year NRM per prior treatment
- AZA
- Induction CT
- AZA + induction CT

AZA monotherapy appears a valid pre-allogeneic HSCT treatment approach

*Azacitidine vs azacitidine + induction CT

AZA & allogeneic HSCT in MDS and AML After HSCT

- AZA alone or in combination with donor lymphocyte infusions may induce durable remissions for patients with acute leukaemia who develop disease recurrence after HSCT\(^1,2\)
- AZA is well tolerated and not associated with exacerbation of GVHD
- AZA increases the expansion of regulatory T-cells after allogeneic HSCT in patients with AML\(^3\)

These data support the further examination of AZA after HCT as a mechanism of augmenting a GVL effect without a concomitant increase in GVHD

Conclusions

- Although high CR rates are achieved with standard chemotherapy, long-term survival rates remain low in patients with high-risk MDS & AML.

- AZA improves OS versus CCR independent of response, adverse cytogenetics, age and comorbidities in high-risk MDS & AML (20–30% blasts).

- The exact role of AZA in AML (>30% blasts) in older patients is being assessed in the AML-001 study.

- AZA has a manageable safety profile and can often be administered in an outpatient setting.

- AZA appears to be a valid pre-allogeneic HSCT treatment approach.

- Early data indicate that post-HSCT AZA may augment a GVL effect without a concomitant increase in GVHD.