IPSS scoring system

- Blood counts
- Bone marrow blast percentage
- Cytogenetics
Age as a modulator of median survival

<table>
<thead>
<tr>
<th>IPSS Group</th>
<th>Median Survival (years)</th>
<th>Age ≤ 60 years</th>
<th>Age &gt;60 years</th>
<th>Age &gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>5.7</td>
<td>11.8</td>
<td>4.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>3.5</td>
<td>5.2</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.2</td>
<td>1.8</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>High</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>
IPSS Risk Categories Distribution

- Low Risk: 31%
- Int-1 Risk: 39%
- Int-2 Risk: 22%
- High: 8%

*Estimated survival and risk of AML transformation

Goals for treatment

- Individual
- Prolong overall survival with best quality
- Prevent disease progression
- Achieve Complete remission
- Minimal side effects of therapy
Treatment Options

- Best Supportive care
- Low dose chemotherapy
- Intensive chemotherapy
- Haemopoietic stem cell transplantation
- Hypomethylating agents
Best Supportive Care

- Blood and platelet transfusions
- GCSF
- Prophylaxis against infection if prolonged neutropenia
- Iron chelation therapy
- No longer the mainstay of MDS therapy
Low Dose chemotherapy

- Low dose cytarabine, subcutaneously
- 20mg/m² daily for 10-14 days
- Disease control
Intensive chemotherapy

- Hospital admission for approximately 4 weeks
- Combination of 2-3 drugs with cytarabine
- Risk of infection
- Risk of delayed recovery of blood counts, marrow aplasia
- Achieve Complete remission (cytogenetic)
- Likelihood of relapse unless consolidated with a stem cell transplant
Haemopoietic stem cell transplantation

- Consolidative procedure after achieving complete remission can cure up to 40% of patients with MDS
- Donor availability
- Reduced intensity conditioned regimes have reduced toxicity
- Infection
- Immune side effects
Hypomethylating agents

- Azacytidine
- Decitabine (deoxy analog of azacytidine)
- Act by inhibiting DNA methyl transferase
- Also called Methyl transferase inhibitors
Promoter methylation of a gene

CpG Island with all ‘C’ unmethylated ON

CpG Island with all ‘C’ methylated OFF

Targeted Methylation ?effect on the gene
Mechanism of action

Silverman, 2001
Trials with Azacytidine

- CALGB 8221 and 8421, Phase II studies established median 4 cycles of treatment needed for a response and subcutaneous use

- CALGB 9221, Phase III randomised control trial compared Azacytidine with Best supportive care
  Silverman et al JCO 2002

- AZA 001, Phase III randomised control trial comparing Azacytidine with Best supportive care, LD cytarabine or Intensive therapy
  Fenaux et al Lancet Oncology 2009
CALGB 9221

1) Observation* → Exit Criteria

- No → Continue until Endpoint
- Yes → Aza C (dose as per arm #2)

2) Aza C 75 mg/m²/d × 7 days q28 × 4

Response
- continue Rx
No response
- off study

QOL

<table>
<thead>
<tr>
<th>Day</th>
<th>M</th>
<th>M</th>
<th>M</th>
<th>M</th>
<th>M</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>15</td>
<td>29</td>
<td>57</td>
<td>85</td>
<td>113</td>
</tr>
</tbody>
</table>

*Minimum duration of observation = 2 months

QOL = Quality-of-life assessment
M = Bone marrow
Aza C = azacytidine S.C.
CALGB 9221 Results

- Azacytidine (99)
  - Complete remission 7%
  - Partial remission 16%
  - Haematological improvement 37%
  - Delayed time to AML by 9 months (12 vs 21 months)

- Best Supportive Care (92)
  - Haematological Improvement 5%
  - Overall survival 11 months
AZA 001

- Multicentre, international
- High risk MDS
- IPSS Int-2 or high
- FAB RAEB RAEB-t or CMML ( <10% blasts
- Previously untreated
- Treatment option predetermined by physician
Aza 001 Trial design

Total 358 patients

Azacytidine 179
- 175 treated

Conventional care 179
- 105 Best supportive care
- 49 Low Dose cytarabine
- 25 Intense chemotherapy
- 102 Treated
- 44 Treated
- 19 treated
Results

- Median Age 69 years, 72% >65 years
- Survival at 2 years was doubled for patients treated with Azacytidine versus conventional care (50.8% vs 26.2%, p<0.0001)
- Time to leukaemia transformation was 17.8 months for azacytidine group versus 11.5 months in the conventional care (p<0.0001)
Overall survival

- Overall survival for Azacytidine 24.5 months vs 15 months with conventional care (p=0.0001)
Results

- Azacytidine was superior
- To BSC
- Low dose chemotherapy
- As effective as intensive chemotherapy
Azacitidine for patients with 7q-/del7q

- Azacytidine prolonged survival to 19.8 months
- AZA001 30 Azacitidine 27 CCR
- Overall survival 13.1 vs 4.6 months
- 33% survived to 2 years
- Standard of care for this subgroup
Administration of Azacytidine

- 75mg/m² x7 days every 28 days
- Subcutaneously
- Average sized person two injections daily
- Rotating sites, abdomen, thighs, upper arms
Side effects of Azacytidine

- Well tolerated
- Increased blood or platelet requirements in the initial cycles
- Nausea
- Constipation/diarrhoea
- Injection site reaction
- Local nodules/bruises
- Febrile neutropenia/sepsis
Concomitant medications

- Antisickness medications
- Topical cream for local reactions
- Laxatives to counter constipation
- Allopurinol to prevent gout
Results
Decitabine

- Analog of Azacitidine
- Phase III study
- 45mg/m\(^2\)/day x3 days q6 weeks IV
- Decitabine n=89, BSC n=81
- 43/89 received less than 2 cycles of decitabine
- CR9\%, PR8\% HI13\%
Low dose decitabine

- IPSS 1.0, CMML, Phase I/II study
- 5-20mg/m2/day for 5/28 days IV
- Dose intensive schedule
- Unlimited cycles of therapy
- CR 34%, PR1%, Marrow CR 24%, 13% HI
- 20mg/m2/day best responses CR39%
- Median survival 19 months
- CMML 19 patients, CR 58%, HI 11%
Combination therapy

- Azacytidine with HDAC inhibitors
- Vorinostat
- Responses in approximately 80%
Algorithm for treating high risk MDS

1. **High/Int-2 patient**
2. **Is a donor available for bone marrow transplantation?**
   - Yes → **Is the patient fit for transplantation?**
     - Yes → **Bone marrow transplantation**
     - No → **Hypomethylating agents**
6. **Chemotherapy**
7. **Clinical trial**
8. **No**
9. **No response**
Summary

- MTI’s should be considered for
- High risk MDS
- Particulary patients with high risk cytogenetics
- Studies on improving outcomes with these drugs either alone or in combination are ongoing
Licensing of Azacitidine

- Licensed by the FDA for all subclasses of MDS
- Azacytidine licensed by the EMEA for
  - Int-2
  - High risk MDS
  - CMML
  - AML with 20-30% blasts
Access to drugs

- Trials NCRN AML 16, CMML
- London cancer new drugs process of approval on going
- NICE review QALY’s too high, company resubmitting
- ETA from local PCT
Acknowledgement

- MRC
- Prof Mufti
- Dr Shaun Thomas
- Patients at KCH and GSTT
Current trials

- MTI prior to stem cell transplant
- MTI maintenance therapy after AML induction therapy
- MTI maintenance therapy after allograft
- Alternative dosing strategies? Lower doses, 5 days a week?
Primary Endpoints

- Primary endpoint overall survival
- Survival by FAB subgroup
- IPSS risk group
- Cytopenia
- Cytogenetics
- -7/del(7q)
- WHO classification
- Serum LDH
Treatment Schedule

- 75mg/m² sc 7/28 days for a minimum of 6 cycles
- LD cytarabine 20mg/m² sc for 14 days/28 days for at least 4 cycles
- Induction chemotherapy with Cytarabine/Daunorubicine, idarubicine or mitoxantrone
- If CR or PR one or two consolidation courses
- Follow up 12 months after last patient enrolled
## WPSS risk groups and survival

<table>
<thead>
<tr>
<th>WPSS Risk Score</th>
<th>WPSS Risk Group</th>
<th>Median overall Survival months</th>
<th>Cumulative probability of leukaemic transformation at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very Low</td>
<td>141</td>
<td>0.03</td>
</tr>
<tr>
<td>1</td>
<td>Low</td>
<td>66</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
<td>48</td>
<td>0.21</td>
</tr>
<tr>
<td>3 or 4</td>
<td>High</td>
<td>26</td>
<td>0.38</td>
</tr>
<tr>
<td>5</td>
<td>Very High</td>
<td>9</td>
<td>0.80</td>
</tr>
</tbody>
</table>
Epigenetics

- Chemical modifications of genes that affect their expression reversibly without alterations in their DNA sequence
- Enable dynamic control of genes in a context driven manner ie in time and space
- DNA methylation
- Histone acetylation
Survival and leukaemic transformation based on IPSS
# HCT comorbidity score and transplant outcomes

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Type of conditioning</th>
<th>Non Relapse Mortality (%)</th>
<th>Relapse (%)</th>
<th>Overall Survival (%)</th>
<th>Relapse free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>MA (n=138)</td>
<td>11</td>
<td>14</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>NMA (n=28)</td>
<td>4</td>
<td>22</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>Group 2</td>
<td>MA (n=176)</td>
<td>24</td>
<td>34</td>
<td>51</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>NMA (n=34)</td>
<td>3</td>
<td>42</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Group 3</td>
<td>MA (n=52)</td>
<td>32</td>
<td>27</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>NMA (n=19)</td>
<td>27</td>
<td>37</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Group 4</td>
<td>MA (n=86)</td>
<td>46</td>
<td>34</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>NMA (n=44)</td>
<td>29</td>
<td>49</td>
<td>29</td>
<td>23</td>
</tr>
</tbody>
</table>

Sorror et al  JCO 2007
Secondary End points

- Time to transform to AML
- Haematological Improvement
- Red cell transfusion independence
## Azacytidine vs best supportive care

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>BSC</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival (months)</strong></td>
<td>21.1</td>
<td>11.5</td>
<td>0.58</td>
<td>0.0045</td>
</tr>
<tr>
<td><strong>Time to transformation to AML</strong></td>
<td>15.0</td>
<td>10.1</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Azacitidine vs Low dose cytarabine

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>LD cytarabine</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>24.5</td>
<td>15.3</td>
<td>0.36</td>
<td>0.0006</td>
</tr>
<tr>
<td>Time to transformation to AML (months)</td>
<td>15.0</td>
<td>14.5</td>
<td>0.55</td>
<td>0.097</td>
</tr>
</tbody>
</table>
## Azacitidine vs Intensive chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Intensive Chemotherapy</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>25.1</td>
<td>15.7</td>
<td>0.76</td>
<td>0.51</td>
</tr>
<tr>
<td>Time to transformation to AML (months)</td>
<td>23.1</td>
<td>10.7</td>
<td>0.48</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Timing of transplantation

Myeloablative transplants
Delayed for low and int-1 MDS net gain of life expectancy
At diagnosis for Int-2 and High risk MDS is beneficial

Cutler et al., Blood 2004
DNA methylation

- 4 bases A, T, G, C.
- 5th base 5 methylcytosine methyl from a s-adenosyl methionine is incorporated into position 5 of the cytosine ring.
- This is restricted to CpG dinucleotides (cytosines that precede guanosine in the DNA sequence)
How does DNA become Methylated?

* Enzymes called DNA methyltransferases (DNMTs) covalently link a methyl group from S Adenosyl Methionine to the 5 position of cytidine residues.
## WHO Prognostic Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Category</td>
<td>RA, RARS, 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 requirement</td>
<td>No</td>
<td>Regular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As per the IPSS subgroups*
Histone Octomer
Silencing of a hypermethylated promoter
DNA methylation in MDS

- In cancer methylation of genes increases
- These are reversibly switched off
- Critical pathways such as cell cycle control, cell death, cellular growth, DNA repair may be affected
- In MDS: p15INK4b, MLH1, ER, may be silenced by methylation and may be critical to disease progression
- Responses to MTI have been linked with demethylation of genes
## Haematological Response

<table>
<thead>
<tr>
<th>Haematological response</th>
<th>Azacitidine</th>
<th>CCR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any remission</td>
<td>29%</td>
<td>12%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Complete remission</td>
<td>17%</td>
<td>8%</td>
<td>0.015</td>
</tr>
<tr>
<td>Partial remission</td>
<td>12%</td>
<td>4%</td>
<td>0.0094</td>
</tr>
<tr>
<td>Stable disease</td>
<td>42%</td>
<td>36%</td>
<td>0.33</td>
</tr>
<tr>
<td>Haematological improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>49%</td>
<td>29%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major erythroid improvement</td>
<td>40%</td>
<td>11%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major platelet improvement</td>
<td>33%</td>
<td>14%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Major neutrophil improvement</td>
<td>19%</td>
<td>18%</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Acknowledgement

- MRC
- Prof Mufti
- Dr Shaun Thomas
- Patients at KCH and GSTT
Disease Factors

- Blast percentage
- Cytogenetics: chromosome 7
- Tempo of disease
- De-novo or secondary MDS
Blast percentage

A. Marrow Blasts

Survival

- <5% 483 pts
- 5-10% 183 pts
- 11-20% 114 pts
- 21-30% 36 pts

B. AML Evolution

- <5% 437 pts
- 5-10% 178 pts
- 11-20% 112 pts
- 21-30% 35 pts
Cytogenetics

A. Survival

- Good: 570 pts
- Intermediate: 112 pts
- Poor: 134 pts

B. AML Evolution

- Good: 521 pts
- Intermediate: 107 pts
- Poor: 131 pts
Cytopenia
**A** Survival (≤ 60 yrs old)

- Low 60 pts
- Int-1 87 pts
- Int-2 49 pts
- High 9 pts

**B** Survival (> 60 yrs old)

- Low 207 pts
- Int-1 227 pts
- Int-2 127 pts
- High 50 pts
Age as a modulator of leukaemic transformation

<table>
<thead>
<tr>
<th>IPSS Group</th>
<th>Median time for 25% Risk of Leukaemia (years)</th>
<th>Age ≤ 60 years</th>
<th>Age &gt;60 years</th>
<th>Age &gt;70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>9.4</td>
<td>&gt;9.4 (not reached)</td>
<td>&gt;9.4 (not reached)</td>
<td>&gt;5.8 (not reached)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>3.3</td>
<td>6.9</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.1</td>
<td>0.7</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>High</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Choice of treatment

- Co-existing conditions
- Cardiac: previous MI, prosthetic valves
- Liver dysfunction
- Pulmonary: COPD,
- Mobility
- Rheumatoid arthritis
- High ferritin levels
Cytogenetic Risk

- **Good Risk**
  - Normal
  - -Y only
  - del5(q) only
  - del 20q only

- **Intermediate Risk: Other anomalies**

- **Poor Risk**
  - Complex (3 or more abnormalities)
  - chromosome 7 abnormalities
Open Chromatin/Transcriptionally Active

Condensed Chromatin/Transcriptionally Inactive

Acetylated Histone tails

Deacetylated Histone tails

Methylated CpG Islands

DNA Methyltransferase

MeCP2/Sin3/HDAC
# IPSS Variables

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score 0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM Blasts</td>
<td>&lt;5%</td>
<td>5-10%</td>
<td>-</td>
<td>11-20%</td>
<td>21-30%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Score 0  Low Risk
- 0.5-1.0 Intermediate I risk
- 1.5-2.0 Intermediate 2 risk
- > 2.5 High risk