HAS THERE BEEN SIGNIFICANT IMPROVEMENT IN THE TREATMENT OF MYELODYSPLASIA?

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SOME OF THE MANY THINGS WE DO NOT KNOW ABOUT THE BIOLOGY OF MDS

- What is the MDS stem cell?

- What happens to the normal hematopoietic precursors in MDS?

- How are they suppressed by the MDS clone?

- Do they recover if the MDS clone responds to treatment?
Some Background Assumptions

• The only cure for MDS is allogeneic transplantation
• The available therapies have low rates of CR and all patients relapse, usually within a year
• There are no tests, clinical or molecular, which predict response to HMA
• Therefore, evaluate for transplant whenever you start treatment with HMA
• The molecular complexity is now more fully understood
• There is no shortage of prognostic models
The Initial Question to Consider in a Patient with Higher Risk MDS

Is he/she a candidate for allogeneic transplantation?
348 Evaluation of Salvage Induction Chemotherapy Regimens in Higher Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia after Hypomethylating Agent Treatment Failure - Ball et al.

n = 366
Many abstracts on “new and improved” prognostic formulae
PROGNOSTIC SYSTEMS IN A NUTSHELL

It is bad to have:

- more blasts
- cytopenias in > 1 lineage
- abnormal and/or complex karyotypes (correlates somewhat with molecular findings)
- to need transfusions
- to have comorbidities

And to be older
Survival Based on WPSS

NOTE: NO ERROR BARS

WHAT MOST PROGNOSTIC CLASSIFICATIONS TELL US

Infrequently provide new biologic hypotheses to be tested – not predictive
The smartest doctor of all....

Dr Time
RESULTS WITH HMA

5 - Azacytidine  Decitabine

CR + PR 21%

CR + PR 17%

(1 yr)
Azacitidine Treatment Prolongs Overall Survival in Higher-Risk MDS Patients Compared with Conventional Care Regimens: Results of the AZA-001 Phase III Study

P Fenaux, MD, GJ Mufti, MD, V Santini, MD, C Finelli, MD, A Giagounidis, MD, R Schoch, MD, A List, MD, S Gore, MD, J Seymour, MD, E Hellstrom-Lindberg, MD, J Bennett, MD, J Byrd, MD, J Backstrom, MD, L Zimmerman, BSN, D McKenzie, MS, CL Beach, PharmD and L Silverman, MD on behalf of the International Vidaza High-Risk MDS Survival Study Group
Overall Survival: Azacitidine vs CCR
ITT Population

Log-Rank \( p=0.0001 \)

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: AZA = 82, CCR = 113

Difference: 9.4 months

And some do OK without treatment
Patents in clinical trials are not representative of the universe of patients with MDS since they are highly selective and exclude patients with organ dysfunction.
WAS ASH HELPFUL?
Combined Treatment with Lenalidomide (LEN) and Epoetin Alfa (EA) Is Superior to LEN Alone in Patients with Erythropoietin (Epo)-Refractory, Lower Risk (LR) Non-Del(5q) MDS

Results of the E2905 Intergroup Study - an ECOG-ACRIN Cancer Research Group Study

AF List, Z Sun, A Verma, JM Bennett, KL McGraw, LA Nardelli, JP Maciejewski, MD, JK Altman, P Cheema, DF Claxton, RS Komrokji, S Luger, R Mattison, T Wassenaar, AS Artz, MD, C Schiffer, MS Tallman
Biological Rationale

• LEN promotes *in vitro* expansion of primitive erythroid precursors.
• In a pilot study of Epo-refractory MDS patients, addition of epoetin alfa (Procrit) yielded erythroid responses in 28% of patients unresponsive to LEN alone, suggesting that LEN overcomes resistance & augments response to rhEpo (Komrokji R, et. al. Blood 2012).
- **Eligibility:** Low/Int-1 IPSS, ESA failure or low response profile, Hgb <9.5 g/dL
- **Stratification:** serum EPO (≥ vs. <500mU/ml), prior ESA (EA vs. DA vs. None)
- Epoetin alfa 60,000 units SC weekly
- Primary Endpoint (EP): MER
- Secondary EP: Time to MER, MER duration, LEN cross-over MER response, candidate response biomarkers (CD45 isoform profile)
E2905 Patient Disposition

N = 163 randomized

Lenalidomide (n = 81)

Withdrawn from treatment (n = 25)
- Adverse event (n = 9)
- Disease progression (n = 7)
- Death (n = 1)
- Patient withdrawn (n = 1)
- Complicating disease (n = 1)
- Alternative therapy (n = 1)
- Other (n = 3)

Discontinued at Week 16 (n = 41)
Crossover to LEN+Epo (n = 34)
Continued LEN (n = 15)

LEN+Epo (n = 82)

Withdrawn from treatment (n = 21)
- Adverse event (n = 10)
- Disease progression (n = 2)
- Death (n = 1)
- Patient withdrawn (n = 1)
- Complicating disease (n = 1)
- Alternative therapy (n = 1)
- Other (n = 3)

Discontinued treatment (n = 32)
Continued LEN+Epo (n = 29)
### E2905 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LEN (n = 81)</th>
<th>LEN+Epo (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>75 (49-89)</td>
<td>73 (47-89)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>55 (68%)</td>
<td>61 (74%)</td>
</tr>
<tr>
<td>Median years from diagnosis (range)</td>
<td>1.5 (0-17)</td>
<td>1.7 (0-18)</td>
</tr>
<tr>
<td>Median RBC transfusion burden, units/28 days (range)</td>
<td>2 (0-7)</td>
<td>2 (0-8)</td>
</tr>
<tr>
<td>Prior Azanucleoside therapy, n (%)</td>
<td>18 (22%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Prior ESA treatment, n (%)</td>
<td>77 (95%)</td>
<td>74 (90%)</td>
</tr>
<tr>
<td>IPSS risk, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>28 (35%)</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>Int-1</td>
<td>51 (63%)</td>
<td>41 (50%)</td>
</tr>
<tr>
<td>IPSS karyotype (central review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>64 (79%)</td>
<td>68 (83%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>14 (18%)</td>
<td>11 (13%)</td>
</tr>
</tbody>
</table>
# E2905 Baseline Characteristics

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<th>LEN (n = 81)</th>
<th>LEN+Epo (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 2008 (central review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>6 (7%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>RARS</td>
<td>18 (22%)</td>
<td>22 (27%)</td>
</tr>
<tr>
<td>RCMD/RCMD-RS</td>
<td>34 (42%)</td>
<td>33 (40%)</td>
</tr>
<tr>
<td>RAEB1</td>
<td>9 (11%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Missing or other</td>
<td>12 (15%)</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>Median BM blast % (range)</td>
<td>2 (0-15)</td>
<td>2 (0-54)</td>
</tr>
<tr>
<td>Median ANC (range), /mm³</td>
<td>2100 (580-6700)</td>
<td>2320 (3-25075)</td>
</tr>
<tr>
<td>Median Platelet count (range), × 10³ mm³</td>
<td>191 (57-727)</td>
<td>226 (55-793)</td>
</tr>
<tr>
<td>Serum Epo [mU/ml]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>167 (11-3048)</td>
<td>143 (19-3264)</td>
</tr>
<tr>
<td>&lt; 500 mU/ml</td>
<td>60 (74%)</td>
<td>58 (71%)</td>
</tr>
</tbody>
</table>
## Fifth Interim ITT Response Analysis

<table>
<thead>
<tr>
<th>Response &amp; Cohort</th>
<th>Arm A (%) LEN</th>
<th>Arm B (%) LEN+Epo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT Analysis [n=163]</strong></td>
<td>N=81</td>
<td>N=82</td>
<td></td>
</tr>
<tr>
<td><strong>MER</strong></td>
<td>9 (11.1)</td>
<td>21 (25.6)</td>
<td>P=0.025</td>
</tr>
<tr>
<td>Minor ER</td>
<td>15 (18.5)</td>
<td>13 (15.9)</td>
<td>P=0.68</td>
</tr>
<tr>
<td>Overall ER</td>
<td>24 (29.6)</td>
<td>34 (41.5)</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Arm A Crossover MER</td>
<td>N=34</td>
<td>7 (21%)</td>
<td></td>
</tr>
</tbody>
</table>
Duration of Major Erythroid Response

Log Rank Test $p=0.37$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TOTAL</th>
<th>FAIL</th>
<th>CNSR</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>13.0</td>
</tr>
<tr>
<td>LEN+EPO</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td>25.4</td>
</tr>
</tbody>
</table>
Conclusions

• Lenalidomide can restore sensitivity to epoetin alfa in Epo-refractory, lower risk-non-del(5q) MDS patients to yield durable and significantly higher rates of erythroid response with combination therapy.

• Combination treatment is safe with no evidence for greater risk of thromboembolic events.

• Erythroid CD45 isoform profile is highly predictive for response to LEN+Epo & may serve as a biomarker for selection of candidates for combination treatment.

• The results of this study support the use of combined lenalidomide and epoetin alfa treatment for patients with IPSS Low or Int-1 risk, non-del(5q) MDS who are unresponsive or refractory to ESAs.
ALTERNATIVE FACTS?

- 224 Lenalidomide with or without Erythropoietin and Granulocyte-Colony Stimulating Factor Shows Efficacy in Patients with Low and Intermediate-1 Risk Myelodysplastic Syndrome with or without Del 5q, Refractory or Unlikely to Respond to Erythropoietin. Results of a HOVON89 Phase II Randomized Multicenter Study.

  van de Loosdrecht et al.
• n = 200 (180 analyzed)
• **No benefit** from adding Epo +/- G-CSF
• HI-E 33% in non del 5q pts
• Median DOR 10 months
• PFS longer in those with HI-E
• 26% HI-E  
  

• 27% HI-E  
  
  Santini et al, JCO 34:2988, 2016

• 23 v 39% (+ EPO)  
  
  Toma et al, Leukemia 30:897, 2016
SO……

• 2 studies to 1 in favor of adding EPO to lenalidomide

• But….
  – The studies were not precisely the same (although probably similar enough)
  – The response rate in the control group in the U.S. “positive” studies was very low and the response rate with EPO in this study was ~ the same as with len alone in the other studies
Optimal Treatment Order of Lenalidomide and Hypomethylating Agents for Lower-Risk Myelodysplastic Syndromes: A Report on Behalf of the MDS Clinical Research Consortium (Komrokji et al)
Retrospective analysis

- 84 pts received len before HMA
- 60 pts received HMA before len

Results – HI-E (first vs. second line)

- HMA
  - 39 vs. 30 % (p= .046)

- Len
  - 20 vs 11% (p= .2)
• **Authors conclusion:** “The order of treatment does not impact overall survival. Lenalidomide should be used prior to HMA if it is to be considered for treatment of anemia in non-del5q LR-MDS”

• **My conclusion**
  – not randomized
  – small number of pts
  – consider the most effective therapy first?
  – practical considerations affect decisions in individual pts
Which HMA?

226 A Randomized Phase II Study of Low-Dose Decitabine Versus Azacitidine in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndromes: A Report on Behalf of the MDS Clinical Research Consortium (Jabbour et al.)

- Bayesian design - 40 A pts, 73 D pts
- 3 day schedule
- No difference in “Overall Improvement Rate” (~50%)
- CR 38% A vs 29% D (NS)
“Early results suggest that low-dose DAC may result in superior EFS compared to low-dose AZA”

My take – Can’t conclude anything, but the trend of the results are consistent with the ~ comparability of the drugs in earlier, non-randomized trials
MOLECULAR CHARACTERIZATION

Mutations and Cytogenetic Abnormalities in 223 Samples with at Least One Mutation.

54 Clinical Relevance of Driver Mutations and Number of Driver Mutations in Patients with Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

Guillermo Montalban-Bravo,
WHY DO MOLECULAR CHARACTERIZATION?

- Sometimes diagnostic in patients with mild cytopenias (CHIP)
- Occasional IDH2 mutation
- P53 (poor response to everything, except possibly decitabine)
- More reason to move to transplant??
69 Genetic Alterations Predict Outcomes in Patients with Myelodysplastic Syndrome Receiving Allogeneic Hematopoietic Stem Cell Transplantation

Lindsley et al
• CIBMTR - 1514 pts (< 20% blasts)
• 127 genes
• Median age 59 years (16% < 40 years)
• ~ 50% - 8/8 matched unrelated donor
Figure 1. Multivariable prognostic model for MDS allo-HCT.

MDS

TP53 mutation
N = 289 (19%)
3 year OS = 20.3%
Median OS = 0.7 years

No TP53 mutation

Age ≥ 40

RAS pathway mutation*
N = 129 (9%)
3 year OS = 24.6%
Median OS = 0.9 years

No RAS pathway mutation

Age < 40

High risk features
1. Therapy-related MDS
2. Platelets < 30 x 10^9/L at HSCT
3. Blasts ≥ 15% at diagnosis

JAK2 Mutation
N = 28 (2%)
3 year OS = 24.6%
Median OS = 0.5 years

No JAK2 or RAS pathway mutation
N = 854 (56%)
3 year OS = 45.3%
Median OS = 2.2 years

≥ 1 High-risk feature
N = 98 (6%)
3 year OS = 49.0%
Median OS = 2.6 year

No high-risk features
N = 116 (8%)
3 year OS = 81.5%
Median OS = n.r.

* RAS-TK pathway: NRAS, KRAS, CBL, PTPN11, NF1, RIT1, KIT, BRAF, FLT3
PROGNOSTIC VARIABLES

• Better outcome
  – Younger age

• Poorer outcomes
  – TP53 mutations (↑relapse)  20%
  – Therapy related MDS
  – Ras pathway mutations (↑relapse)  25%
  – JAK2 mutations (↑TRM)  25%