TP53 status predicts response to decitabine in AML and MDS

Fellow: Joe Hiatt
Faculty discussant: Roland Walter
Hematology Fellows Conference
3/10/2017
Case 1:

79M w/ HTN, HLD

New dx of AML w/ myelodysplasia-related features, complex cytogenetics, 22% blasts

TRM: ~40 (ECOG 2, albumin 2.7, creatinine 1.3)
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Case 2:
56M w/ HIV/ART, sarcoid, DM
New dx of MDS w/ ringed sideroblasts, complex cytogenetics, <5% blasts
TRM: 5.9 (ECOG 1, albumin 3.5, creatinine 1.3)
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<thead>
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<th>Case 1:</th>
<th>Case 2:</th>
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**What are the treatment options and expected outcomes?**
Multiple therapies with variable risk:benefit

- High intensity cytotoxic chemo (7+3-like)
- CPX-351
- Clinical trial
- Low-dose chemo
- “Hypomethylating” agent
- Best supportive care

*not to scale
Risk calculators predict poor outcomes

A

<table>
<thead>
<tr>
<th>TRM Score</th>
<th>SWOG Patients (years of age)</th>
<th>MDA Patients (years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 60</td>
<td>≤ 60</td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0–3†</td>
<td>7 of 68</td>
<td>10</td>
</tr>
<tr>
<td>4–6‡</td>
<td>27 of 218</td>
<td>12</td>
</tr>
<tr>
<td>≥ 7§</td>
<td>35 of 113</td>
<td>31</td>
</tr>
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</table>

Complex cytogenetics predicts poor outcomes

AML

Complex cytogenetics predicts poor outcomes


Schanz et al, JCO 2012; 8:820-829.
TP53 implies even worse prognosis in AML

Complex Karyotype (34%)

TP53 implies even worse prognosis in AML

Complex Karyotype (34%)  All comers (6%)


**TP53** also implies inferior prognosis in MDS

*TP53* also implies inferior prognosis in MDS


TP53 also implies inferior prognosis in MDS

Risk calculators and cytogenetics are prognostic>predictive

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Correlating response to decitabine with mutations

116 pts with AML (new dx and age>60), relapsed AML, MDS (transfusion dependent and >10% blasts); ECOG 0-2

Decitabine 20 mg/m² given d1-10 of 28d cycle (except for 8 pts who received d1-5 of 28, 3 w/ panobinostat)

Prospective (mostly), with drug level assessment, frequent bone marrow bx, genotyping and methylation

Outcome: Response (by IWG criteria); (survival)
Patients are older, AML > MDS, *TP53* wt > mut

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=116)</th>
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</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>68 (59)</td>
</tr>
<tr>
<td>Age at diagnosis — yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>74</td>
</tr>
<tr>
<td>Range</td>
<td>29–88</td>
</tr>
<tr>
<td>Disease — no. (%)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>54 (47)</td>
</tr>
<tr>
<td>Relapsed AML</td>
<td>36 (31)</td>
</tr>
<tr>
<td>MDS</td>
<td>26 (22)</td>
</tr>
</tbody>
</table>
TP53 mutation is associated with high response rate
Blasts go down, counts don’t always come back

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=116)</th>
<th>TP53 Mutations (N=21)</th>
<th>Wild-Type TP53 (N=78)</th>
<th>TP53 Not Evaluated (N=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blast clearance &lt;5% blasts</td>
<td>53 (46)</td>
<td>21 (100)</td>
<td>32 (41)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
TP53 goes down (not to zero, always comes back)
Hypomethylation occurs regardless of response
Hypomethylation occurs regardless of response
Response and transplant associate with survival

A  Overall Survival

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>CR/CRi/mCR</th>
<th>PR/SD</th>
<th>PD/NA</th>
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<tr>
<td>CR/CRi/mCR</td>
<td>53 44 20 9 4</td>
<td></td>
<td></td>
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<tr>
<td>PR/SD</td>
<td>36 17 10 8 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD/NA</td>
<td>27 15 11 5 3</td>
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Response and transplant associate with survival

A Overall Survival

![Graph showing overall survival with different outcomes and survival rates.]

E Survival According to Stem-Cell Transplantation

![Graph showing survival rates with transplantation and no transplantation.]

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<td>4</td>
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<tr>
<th>No. at Risk</th>
<th>Transplantation</th>
<th>No transplantation</th>
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<tr>
<td>32</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
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<td>9</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
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Karyotype and mutant *TP53* do not predict survival
Karyotype and mutant TP53 do not predict survival

Except in MDS, where mutant TP53 is adverse (HR=21.4, CI 1.8-250)
Major findings of Welch et al

100% of patients with *TP53* mutations had bone marrow blast clearance compared to ~40% without *TP53* mutations

*TP53* was always cleared from marrow, but never completely, and always came back

Hypomethylation was widespread and independent of response

“Adverse” cytogenetics and *TP53* not adverse, except for *TP53* in MDS
TP53 doesn’t predict response in similar scenarios

Montalban-Bravo et al, NEJM Letter to Editor, 2/23/2017:

- Four studies with “hypomethylating agent” and TP53 status (532/550 pts have MDS)
- No assoc of TP53 w/ response; worse survival w/ TP53
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Welch et al respond:

- (almost entirely) MDS vs (mostly) AML
- 5-azacytidine or decitabine x5d vs decitabine x10d
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Welch et al respond:

- (almost entirely) MDS vs (mostly) AML
- 5-azacytidine or decitabine x5d vs decitabine x10d

Is 10d of decitabine now the “preferred regimen” for poor risk cyto AML?

Is decitabine “less effective” for intermediate risk cyto AML?

Is count recovery or MRD as meaningful after hypomethylating agent? Should response definition be specific to treatment?
Decitabine was ________ for Dr W’s 79M w/ AML

79M AML w/ MDS-related features, complex karyo

TRM: ~40 (ECOG 2, albumin 2.7, creatinine 1.3)
Decitabine was evaluated for Dr W’s 79M w/ AML

79M AML w/ MDS-related features, complex karyo

TRM: ~40 (ECOG 2, albumin 2.7, creatinine 1.3)

First-line therapy (8/2013): CPX-351 at 66U/m2 on prot. 2642

Partial remission after two cycles; Progression after third cycle

Second-line (1/2014): decitabine 20 mg/m2 x10d

Morphologic CR with count recovery after 3 cycles
Decitabine was effective for Dr W’s 79M w/ AML

79M AML w/ MDS-related features, complex karyo

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Morphologic CR with count recovery after 3 cycles

Received decitabine for 15 cycles before eventual decompensation, transition to hospice July 2015
What about our younger patient with MDS?

56M w/ HIV/ART, sarcoid, DM

New dx of MDS w/ ringed sideroblasts, low blast burden, and complex cytogenetics

*TRM: 5.9 (ECOG 1)*
What about our younger patient with MDS?

56M w/ HIV/ART, sarcoid, DM

New dx of MDS w/ ringed sideroblasts, low blast burden, and complex cytogenetics

TRM: 5.9 (ECOG 1)

TP53 status… pending.
Many diseases, many treatments, some thoughts

Presence of complex karyotype +/- TP53 mutation may predict superiority of decitabine x10d compared to other regimens

Validation in larger cohorts with comparative treatment arms is needed

Why is TP53 mutation sensitizing to decitabine x10d?

Current prognostic/predictive paradigms (e.g. IPSS-R, karyotype, TRM, response criteria, MRD~outcome) based on experience with “7+3”-like regimens

Will these paradigms hold as new treatments are developed?
Acknowledgments

Roland Walter for generous assistance with preparation!
Tim Ley and John Welch for answering nagging questions