Do post-transplant hypomethylating agents prevent or only postpone relapse?

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postpone
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**Disclosure of Conflict of Interest (List)**

<table>
<thead>
<tr>
<th>Celgene</th>
<th>Consultant</th>
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Detailed review and discussion

NCI 2nd Relapse Symposium

Kroger, Giralt, Bishop, Wayne

3 manuscripts
Biology of Blood and Marrow Transplantation 2013

Manuscripts edited and organized by Battiwalla and Hardy
If the effect is directed against the disease itself, then history is against us

1- Most maintenance interventions in myeloid malignancies either fail altogether or succeeded only in prolonging event-free survival, but not survival.

2- Same can be said about a significant number of donor versus no donor comparisons in AML.
## Maintenance therapy in AML

<table>
<thead>
<tr>
<th>Study</th>
<th>No. pts</th>
<th>Regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON*</td>
<td>147</td>
<td>LoDAC x 8 cycles vs observation</td>
<td>DFS better; no difference in OS</td>
</tr>
<tr>
<td>GAMLCG†</td>
<td>339</td>
<td>TAD for 3 years vs consolidation x 1 cycle</td>
<td>RFS better with maintenance</td>
</tr>
<tr>
<td>Brune M</td>
<td>320</td>
<td>IL-2 plus Histamine</td>
<td>LFS: 40% vs 26%</td>
</tr>
</tbody>
</table>

Lowenberg et al. *J Clin Oncol*. 1998;16:872-881; DFS was 13% vs 7%

†Buchner et al. *J Clin Oncol*. 2006;24:2480-2489. RFS 48% vs 43%

NEWLY DIAGNOSED AML
(OR RELAPSED AML)

CONSOLIDATION THERAPY

INDUCTION THERAPY

RANDOMIZATION

DECITABINE

LDAC

CONTINUED CHEMOTHERAPY

OBSERVATION

STRATIFICATION FOR CR1:

≤60 vs. > 60 YEARS
Intermediate vs. Poor risk Cytogenetics
Relapse and EFS

Boumer and Ravandi

[Graphs showing incidence of relapse probability and event-free survival probability over months for different maintenance treatments, with statistical significance values of p = 0.7 and p = 0.9.]
Lets then assume the effect is mostly mediated by donor cells

1. Active against the disease.
2. Not too toxic.
3. Not myelotoxic (or with tolerable myelotoxicity).
4. Can be given early after transplant.
5. Influence donor cells favorably.
6. Increase immunogenicity of malignant cells.
Time tunnel

- Hypomethylating Agents in 2002

- increase antigenic density of surface determinants of mature myeloid cells and increase expression of MHC-class I molecules, HLA-DR and beta-2-microglobulin.

- γ Globin HbF gene promoter methylation decreased, fetal hemoglobin levels increased, and hemoglobin levels improved with decitabine 0.2 mg/Kg 1-3 times weekly

Saunthararajah Y; Blood 2003; 102:3865

Pinto A. Blood 1984; 64: 922-929.
Hypomethylating Agent dose

Classic idea : Allogeneic stem cell transplant context (with BuCy):
- decitabine 400 mg / m², 600 mg / m² and 800 mg / m²


Phase 1 study of low-dose prolonged exposure schedules of decitabine in hematopoietic malignancies.

5-20 mg/m²  5 days/week × 2 weeks
  15 mg/m² best  -  30 times < MTD


Duration of exposure  -  longer may be better.

Dose – is low better, same or worse ??
Hypothesis

Low dose 5-Azacitidine will decrease the relapse rate after allogeneic transplantation.

Study Aim

To determine the safest dose and schedule combination of azacitidine given after allogeneic transplant. (doses of 8 – 40 mg / m2 daily x 5 days)
Global DNA methylation (LINE assay (bisulfite pyrosequencing)) : No dose was found to significantly affect global methylation (Garcia-Manero’s laboratory)

Less chronic GVHD with longer exposure (max of 4 cycles)

MTD : 32 mg / m2 X 5 days
Hypothesis
Low dose 5-Azacitididine will decrease the relapse rate after allogeneic transplantation.

Study Aim
Randomized comparison of 1 year maintenance with low-dose AZA 32 mg/m2 daily X 5 days, in 28 day cycles, for 1 year, versus no maintenance

- - as of 9/2013 : n = 123 patients

Designed to detect a prolongation in EFS
The issue of sustainability of the effect

- is the intermittent administration of a drug enough to induce a sustained effect on donor cells.

– models would indicate that epigenetic effects do not persist after pharmacologic intervention is stopped.

- If the main effect of low dose azacitidine is to induce tolerance and, inhibitory, regulatory T cells, could we actually increase the risk of relapse ??
AzaC treatment of mice that underwent a transplantation with delayed allogeneic T cells mitigates GVHD. (A) Schema of the experiments.
FOXP3 Demethylation in amplicon 9 occurs during low-dose AZA maintenance therapy

Simrit Parmar

7-color flow for: CD4, CD8, CD14, CD16, CD19, CD25, CD127
Immune reconstitution during low-dose AZA maintenance

Krishna Komanduri, MD
Eric Wieder, PhD
University of Miami
### Patient and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=230)</th>
<th>AZA&lt;=3 cycles (n=48)</th>
<th>AZA&gt;3 cycles (n=37)</th>
<th>P (controls X AZA&gt;3 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>52</td>
<td>60</td>
<td>52</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Ablative preparative regimen</strong></td>
<td>63%</td>
<td>25%</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Disease status (remission (CR1/CR2)/ active disease)</strong></td>
<td>64%/36%</td>
<td>31%/69%</td>
<td>41%/59%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>AML/MDS</strong></td>
<td>95%</td>
<td>96%</td>
<td>86%</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Second allo HSCT</strong></td>
<td>7%</td>
<td>15%</td>
<td>22%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Peripheral blood graft</strong></td>
<td>86%</td>
<td>75%</td>
<td>70%</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>&lt;10/10 HLA match</strong></td>
<td>4%</td>
<td>11%</td>
<td>13%</td>
<td>P=NS</td>
</tr>
<tr>
<td><strong>Tacrolimus-based GVHD prophylaxis</strong></td>
<td>98%</td>
<td>92%</td>
<td>89%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>aGVHD incidence (grade II-IV/III-IV)</strong></td>
<td>10%/2%</td>
<td>17%/11%</td>
<td>25%/3%</td>
<td>0.01 (gd II-IV)</td>
</tr>
</tbody>
</table>
Cumulative incidence of cGVHD. 6-month landmark analysis.

Rima Saliba

Similar survival
A cautionary reminder:

most interventions that decreased the incidence of chronic GVHD in our field led to more relapses
Rephrasing the question

Does it prevent relapse at all ??

May be.

But we will have to work hard to prove it.
Conclusions

There is no clear cut evidence that low dose hypomethylating agent after allogeneic transplant will increase the cure rate. Could a metronomic approach (with oral aza) improve things?

I will support wholeheartedly the concept that the post transplant scenario, once the realm of GVHD trials, may provide an ideal arena to improve disease control now that new therapies (cellular and otherwise) are available.

However, one has to consider if it will be more meaningful to concentrate on targeted therapies after transplant, instead of using agents with unclear mechanism of action.
Stem Cell Transplantation Program

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Phase I study (years 2005-2007)
Overall survival (minimum follow up of 3 years)
80% patients NOT in CR at transplant
N = 47 - post-transplant Vidaza (1 – 4 cycles)

Overall Survival

Median OS=28 months
5 year OS=40%

Gabriela Rondon, Julienne Chen, Betul Oran