Novel Strategies for Preventing Relapse after Allogeneic Transplantation for MDS

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Disclosures

Celgene: research grant

Otsuka: advisory board
My presentation will focus on:

- maintenance of remission
- possible role of azacitidine in this setting
- will not discuss developments in preparative regimen
- Therefore will not be a comprehensive review!
- Will make analogies and extend conclusions to MDS, from AML studies.
Age-specific incidence rates (per 100,000)

- Less than 50: 0.5
- 50-59: 5.3
- 60-69: 15
- 70-79: 49
- 80 and over: 89

The aging conundrum

1- Most patients with MDS are older than 55 years old.

2- Relapse / refractoriness incidence increases with aging.
Treatment of relapsed and refractory MDS and AML

Abandon hope, all ye who enter here.

*Dante Alighieri. Inferno* (III, 1, 9)
Why prevent relapse?

1- For obvious reasons!

2- Treatment of relapse post transplant is suboptimal!
Treatment of FLT3-ITD Positive AML Relapsing After Allogeneic Hematopoietic Stem Cell Transplant (HSCT) with Sorafenib

Survival from relapse

Manish Sharma
TRM and relapse of patients 40+ years receiving nonmyeloablative allogeneic HSCT for AML and MDS, 1995-2005, by age

**TRM**

![Graph showing TRM for different age groups: 65+ yrs, 60-64 yrs, 55-59 yrs, 40-54 yrs.](Tp08_10.ppt)

**Relapse**

![Graph showing relapse for different age groups: 65+ yrs, 60-64 yrs, 55-59 yrs, 40-54 yrs.](Tp08_10.ppt)

*p=0.66*  
*p=0.87*

**Blood 2008;112 (11):135a (Abstract #346)**
The dose intensity conundrum.
Allogeneic Marrow Transplantation in Patients With Acute Myeloid Leukemia in First Remission: A Randomized Trial of Two Irradiation Regimens


*Blood, Vol 76, No 9 (November 1), 1990: pp 1867-1871*

Fig 4. Probability of surviving relapse-free after transplantation.
Strategies for Preventing Relapse

1- Pre-emptive treatment of relapse
   - minimal residual disease-based (PCR, flowcytometry etc)
   - based on pre-transplant high-risk parameters

2- Maintenance of remission
   - based on pre-transplant parameters

3- Improve conditioning regimen.

4- Select patients.
MRD Based Preemptive 5–Aza Treatment in patients with MDS or AML after allogeneic HSCT – Results of the “RELAZA” Trial


University Hospital “Carl Gustav Carus”
Technical University of Dresden, Dresden, Germany
Study design - Therapy

Tx  d56  every 4-8 weeks CD34-donor chimerism

- Pt eligibility criteria for treatment:
  - CD34⁺-DC dropped < 80%
  - Still in CR

- AZA 75 mg/m²/day s.c. days 1–7, q28d x 4
Response after AZA cycles 1–4

Median age = 58 years
Conditioning: RIC 18/20
MDS/2\textsuperscript{nd} AML = 6
CR1 = 5
Prim. Refr. = 2

AZA cycles 1–4 (N = 20)

- **Major response**
  - CD34\textsuperscript{+}DC > 80%
  - (n = 10; 50%)

- **Minor response**
  - CD34\textsuperscript{+}DC still < 80%, but no relapse
  - (n = 6; 30%)

- **Relapse**
  - between cycles 2 and 4
  - (n=4; 20%)

Acceptable toxicities
Strategies for Preventing Relapse

1- Pre-emptive treatment of relapse
   - minimal residual disease-based (PCR, flowcytometry etc)
   - based on pre-transplant high-risk parameters

2- Maintenance of remission
   - based on pre-transplant parameters
The maintenance agent

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.

Trial design

1- Dose may not be the same as in other scenarios!
2- Phase III trial mandatory given multiples biases, confounding variables etc
Low dose azacitidine to treat relapsed AML / MDS after allogeneic transplant

- Relapsed AML / MDS after allogeneic HSCT:
  - doses of 16 – 40 mg/m² for 5 days in 28-30-day cycles induced complete remission and reversion to full donor chimerism in 20-25% of patients treated (n=19)

Jabbour et al. Cancer. 2009 Feb 20;115(9):1899-1905
Combining Azacitidine (5-Aza) and Donor Lymphocyte Infusions (DLI) as First Salvage Treatment in Patients with AML or MDS relapsing after allogeneic hematopoietic stem cell transplantation:

An interim analysis from the AZARELA-trial (NCT-Nr.: 00795548)

Thomas Schroeder, MD
Dept. of Hematology, Oncology and Clinical Immunology
University Hospital Duesseldorf
02/2009 - 05/2010 30 pts in 6 centers

Data analysis available for 25 pts (safety 21 pts)

Median Follow up 100 days (25 - 485)

5-Aza : median of 3 courses
DLI = median of 1 course
CR/Cri : 20%
Ideal maintenance agent

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.

Trial design

1- Dose may not be the same as in other scenarios!
2- Phase III trial mandatory given multiples biases, confounding variables etc
Hypomethylating Agents

- induce phenotypic modification of leukemic cells, including reduction of CD13 and CD33 expression,

- increase antigenic density of surface determinants of mature myeloid cells such as CD16 and CD11c,

- increase expression of MHC-class I molecules, HLA-DR and beta-2-microglobulin.

Pinto A. Blood 1984; 64: 922-929.
Azacitidine affects expression of the LAAs NE and P3 (PR1 precursors) in leukemia cell lines.
Hypomethylating Agents – Potential Effects

- Increased expression of tumor-associated antigens ie CTA (Roman-Gomez, 2007) Tatjana Stankovic et al. Goodyear et al.
- Increased expression of KIR ligands on hematopoietic cells (Liu, 2009)
- Recovery of reduced expression of HLA class I, II and III antigens on tumor cells (Campoli & Ferrone, 2008) (Pinto et al – 1984)
- Increased expression of known Minor antigens (Hambach, 2009)
- Increased FoxP3 expression and $T_{reg}$ generation (Polansky, 2008) (Choi et al. 2010) (Sanchez-Abarca et al. 2010)
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 x 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.
Non-randomized dose and schedule finding study

Clinical Trials. 2007; 4:113-124.
Patients in complete remission after HSCT

- Serum creatinine <1.6 mg/dL and
- Serum bilirubin <1.6 mg/dL and
- SGPT ≤ 3 X upper limit of normal and
- Platelet count greater than 15,000/mm³
- ANC > 1,000/mm³
- No active bleeding
- No uncontrolled acute GVHD
- No acute GVHD grade III or IV
- No life-threatening infection.

**Treatment Plan**: 5-azacitidine was given in up to four monthly cycles; each patient is assigned to a dose and a schedule (for example, study started with 8 mg/m² x 1 cycle)
GVHD prophylaxis: tacrolimus from day –2 (levels at 5-15 ng/mL) and mini-methotrexate 5 mg/m² on days +1, +3, +6 and +11.

MUD: Rabbit ATG 0.5 mg/Kg day –3, 1.25 mg/Kg days –2 and –1.

CD33 positivity by flow cytometry in > 20% of leukemia cells.

Leukemia. 2008; 22(2):258-64.
Protocol 2005-0417

Patient characteristics

Median age = 60 ( range, 24 – 67 )

Median comorbidity score : 3 (range, 0-8)

Chemotherapy regimens prior to HSCT (median = 2)

AML from MDS : 73%        MDS : 5%        AML : 22%

Median bone marrow blasts at transplant : 10% (0-86%)

CR at HSCT : 20%

Cancer 2010.
Global DNA methylation (LINE assay (bisulfite pyrosequencing)):
No dose was found to significantly affect global methylation

Guillermo Garcia-Manero’s laboratory

Leandro Silva
Azacitidine maintenance – MTD : 32 mg/m²

Survival - patients that received AZA

Median follow-up = 16 months

Fitted Bayesian logistic regression model for chronic GVHD (N=43; 2 patients were inevaluable due to early deaths).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Posterior 95% Credible Interval</th>
<th>Probability of a Beneficial Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.582</td>
<td>0.779</td>
<td>-0.887</td>
<td>2.111</td>
</tr>
<tr>
<td>Azacitidine dose</td>
<td>0.0145</td>
<td>0.036</td>
<td>-0.083</td>
<td>0.057</td>
</tr>
<tr>
<td>Number of cycles</td>
<td>-0.439</td>
<td>0.311</td>
<td>-1.073</td>
<td>0.159</td>
</tr>
</tbody>
</table>
Azacitidine maintenance

- Azacitidine was well tolerated at the doses studied here
- Approximately 60% of the patients (heavily pre-treated, refractory etc) were able to receive at least one cycle
- At least 4 cycles at 32 mg/m² could be delivered, and there is was no reason to believe we could not proceed for a longer period of time
- Then, RANDOMIZE!
Azacitidine maintenance
-randomization: standard of care X
AZA at 32 mg/m² monthly for 1 year

N = 34
Median age : 51 (20-70)
35% MDS or MDS-AML
55% unrelated donor HSCT
70% not in CR at transplant
26% second transplant
Planned : 250 patients
Reinventing post transplant maintenance for MDS

- immunologic approaches
**“TCR-like” anti-PR1/HLA-A2 antibody (8F4)**

8F4 mouse monoclonal IgG2a (anti-PR1/HLA-A2)

- **Binding affinity:** $K_D = 9.9$ nM to PR1/HLA-A2 monomers
- **Binding region:** $P_1$ (Val) of PR1 + aa169-171 of HLA-A2 $\alpha_2$ domain
- **Cross reactivity:** does not bind PR1 alone, P3, NE, other pep/MHC
- **Detection:** < 1,000 PR1/HLA-A2 molecules/cell

Molldrem et al.
GM-CSF Secreting Leukemia Cell Vaccination after Allogeneic Reduced Intensity HSCT for Advanced Myeloid Malignancies

Vincent T. Ho MD, Glenn Dranoff MD, Haesook Kim PhD, Matthew Vanneman, Mildred Pasek, Corey Cutler MD, Joseph H. Antin MD, Jerome Ritz MD, Robert J Soiffer MD

American Society of Hematology Meeting
San Francisco, CA
December 12, 2008
Conclusions

- Several groups are investigating other approaches to improve preparative regimen and graft anti leukemia function.

- Maintenance therapy may contribute to the treatment of patients with MDS, but this approach is experimental.

- 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.
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