The Role of Natural Killer Cells in Cancer and Transplantation

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How can we best exploit NK cells?

Adoptive Transfer  ?  Transplant

Pros and cons

Safer
Transient
Can expand in vivo (IL-2)

More TRM
Permanent
Too risky 2°
GVHD risk
## AML Transplant Trials Based on Promoting NK Cell Alloreactivity

<table>
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<tr>
<th>Transplant</th>
<th>Graft</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Davies et al, Blood 11/2002</td>
<td>URD KIR-L Mismatch</td>
<td>UBM</td>
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<td>Giebel et al, Blood 8/2003</td>
<td>URD KIR-L Mismatch</td>
<td>In Vivo TCD</td>
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Killer-Immunoglobulin Receptor (KIR) Gene Locus

Group-A Haplotype: Absence of 2DS2, 2DL5, 2DS1, 2DS3, 2DS5, 3DS1

Group-B Haplotypes: Presence of at least one of above
How can we best exploit NK cells?

Adoptive Transfer ? Transplant

Pros and cons
Outpatient Subcutaneous IL-2 Promotes In Vivo NK Cell Expansion

…but NK cells are not maximally activated

Miller et al, Biol Blood Marrow Transplant 3:34, 1997
Autologous NK Administration in Cancer Patients

Recovery from autologous HCT

IL-2

NK cells more activated using this approach
 NK Cell-based Autologous Immunotherapy to Prevent Relapse (HD, NHL, BC)

*Burns et al, Bone Marrow Transplant, 32:177-186, 2003*

**Conclusions**

Enhanced activation of NK cells

A matched paired analysis with our data and data from the IBMTR showed no apparent efficacy (survival or time to disease progression)
Hypothesis:
Autologous NK Cell Therapy Failed Due to Inhibitory Receptors that Recognize MHC

- **KIR - MHC class I match** -> No Killing
- **KIR - MHC class I mismatch** -> Lysis occurs
Related Donor Haploidentical NK Infusions After High Dose Chemotherapy

PB

TCD IL-2

NK

HD Rx

Cy 60 mg/kg x 2
Flu 25 mg/m² x 5
2-8 x 10⁷ MNC/kg

IL-2

10 MU QOD x 6
Patients and Eligibility

- Poor prognosis AML
  - Primary refractory disease
  - Relapsed disease not in CR after 1 or more cycles of standard re-induction therapy
  - Secondary AML from MDS
  - Relapsed AML ≥ 3 months after HCT.
- No active infections
KIR Ligand Mismatched Donor Correlates with Achieving AML CR (5 of 19=26%)
Higher Numbers of Functional NK Cells in Patients with CR After Adoptive Transfer

Miller et al, Blood 105:3051, 2005
Hi-Cy/Flu Induces In Vivo Expansion of Donor Cells

% Donor

Day after NK cell infusion

AML Hi-Cy/Flu
Renal - Flu

0 1 2 7 14 28
Hi-Cy/Flu Induces Endogenous IL-15 which Correlates with In Vivo NK Cell expansion
Hypothesis

The best strategy may be to combine adoptive transfer and in vivo expansion followed by HCT

Adoptive Transfer + Transplant

The best of both worlds?
Umbilical Cord Blood

- 100-150 ml cord blood
- Usually discarded
- High concentration of hematopoietic and NK cell progenitors
- Stem cell source for related donor transplant
Cord Blood is Rich in NK Cell Precursors

Triple UCB NK Infusion and Transplant
(intensive conditioning)

Unit #1

IL-2

NK

Units #2, #3

IL-2

Intensive Conditioning
Late Engraftment after Triple UCBT

UCB NK  |  DCBT  |  IL2

From DCBT

UCB NK  |  DCBT  |  IL2

Day
Early Engraftment after Triple UCBT

From UCB NK
Where do we go from here?

• Improve patient selection
• Improve NK cell activation  
  – Interrupt inhibitory receptor mechanisms
• Increase target sensitivity  
  – Bortezomib
NK Cell Target Cell

Inhibitory Receptors

- CD94
- NKG2A
- HL-A-E
- SHP-1
- KIR3DL2
- KIR3DL1
- KIR2DL1
- KIR2DL2
- KIR2DL3

Target Cell

- HLA-A3/11
- HLA-Bw4
- HLA-C2
- HLA-C1
- HLA-E
- HLA-A

Verneris and Miller
NKG2A/KIR Expression Distinguishes NK Cell Repertoire

KIR⁻/NKG2A⁻ subset: 19.4 ± 2.8% of CD56⁺dim NK cells healthy donors (n=26)

Cooley et al
Sensitization of Tumor Cells to NK Cell-Mediated Killing by Proteasome Inhibition

William H.D. Hallett,* Erik Ames,* Milad Motarjemi,* Isabel Barao,* Anil Shanker,†
David L. Tamang,* Thomas J. Sayers,† Dorothy Hudig,* and William J. Murphy*‡

JI 180:163-170, 2008
Conclusions

- NK cells are important in cancer therapy and transplantation
- KIR B donor haplotype improves RFS after unrelated T-replete HCT for AML
- We are currently treating refractory AML with NK cells + HCT
  - Myeloablative regimen with UCB NK + UCB HCT
  - RIC with adult NK cells and CD34⁺ cells
- New strategies to improve NK cell killing in vivo may improve efficacy
# P01 (PI: Jeffrey S. Miller)

“NK Cells and their receptors in unrelated donor transplantation”

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