Natural Killer cells and Hematopoietic Stem Cell Transplantation
Jeffrey S. Miller, M.D.

University of Minnesota Cancer Center
Associate Director of Experimental Therapeutics
Division of Heme/Onc/Transplant
Minneapolis, MN
NK cells are important

- Cancer treatment and tumor surveillance
- Infection disease control
- Autoimmunity
- Pregnancy (placental angiogenesis)

**NK cell functions**

- Killing targets
- Produce cytokines
  - Interferon-\(\gamma\)
  - Tumor necrosis factor
  - Many others
NK cells after transplant are increased

Cooley et al. Blood 106:4370, 2005
Chr. 19 determines the personality of NK cells: Killer-immunoglobulin receptor (KIR) gene locus

NKG2 family recognizes HLA-E

From Peter Parham
NK cells are very different after URD HCT

Recipients have
- < KIR
- > CD56<sup>+</sup>bright
- > NKG2A
- < Function

Cooley et al
NKG2A/KIR expression distinguishes populations of CD56^{+\text{dim}} NK cells

KIR^{-}/NKG2A^{-} subset: 19.4 ± 2.8% of CD56^{+\text{dim}} NK cells healthy donors (n=26)

These cells do not kill targets or make IFN, thus are hyporesponsive (immature)

Hypothesized NK cell development schema

**Marrow**
- HSC=CD34+/Lin-/CD38-
- CD34+/CD7- CD56-
- Lymphoid committed progenitor
- CD34-/CD7- CD56-
- NK cell precursor
- CD56- KIR-

**LN Stage 4**
- NK cell commitment
- CD56 KIR-
- IFN-γ producing NK

**Blood Stage 5 & 6**
- MatureFc+ cytotoxic NK
- CD56bright KIR-
- CD56dim KIR+

**NK precursors left shifted into the blood after transplant?**
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

PB

IL-2

NK

IL-2

NK cells more activated using this approach
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).

NK cell-based autologous Immunotherapy to prevent relapse (HD, NHL, BC)

Burns et al, Bone Marrow Transplant, 32:177-186, 2003
Hypothesis: Autologous NK cell therapy failed due to inhibitory receptors that recognize MHC.

- **Auto**
  - NK
  - KIR
  - MHC class I match -> No Killing

- **Allo**
  - NK
  - KIR - MHC mismatch -> Lysis occurs

**To Kill or not to kill**
AML Transplant trials based on promoting NK cell alloreactivity

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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
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 (n=19)
  - 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%)
CR patients had higher numbers of functional NK cells after haplo NK cells after haplo NK cells after haplo NK cells.

Miller et al, Blood 105:3051, 2005
In vivo expansion of haploidentical NK cells in AML

**HLA-B7**

**B-act**

**Donor Specific HLA-A31**

**β-actin**
Circulating donor cells were functional NK cells 14 days after Haplo NK cell infusions

Verified by VNTR and G-banding
Hi-Cy/Flu induces in vivo expansion of donor cells (all patients by prep)
Hi-Cy/Flu induces endogenous IL-15 which correlates with in vivo NK cell expansion
Interpretation of cytokine data

- Every time we give lymphodepleting chemotherapy (±TBI), we see a sustained surge in endogenous IL-7 and IL-15.
- May explain high fevers when adding exogenous IL-2 in this setting.
Questions

• Why NK cells don’t expand in everyone?

• Would other cell sources be superior to adult blood NK cells?
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

Testing this population clinically
Patient Eligibility

- Age 2-45 years
- Refractory AML
Conclusions

• NK cells are important in cancer therapy and transplant.
• Better methods to optimally activate NK cells are still needed for refractory AML patients.
• KIR genotyping may be of value in selecting donors in addition to HLA-typing.
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NK PPG working group