ENGAGING NK CELLS IN T-CELL LYMPHOMA

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Introduction to pertinent NK cellular biology

Augmentation of antibody-dependent cellular cytotoxicity (ADCC)
  - ADCC-inducing mAbs

Autologous and allogenic NK cells
  - *Ex vivo* activated or genetically modified NK cells
  - Chimeric antigen receptor (CAR)

In vivo NK cells engagers
  - Bispecific Abs
**TUMOR MICROENVIRONMENT** - innate and adaptive immunity act as a complementary network of self-defense against foreign threats

Natural Killer (NK) Cells

- NK cells were initially identified through their ability to kill tumor cells
  - NK cell infiltration in tumor tissue is associated with better disease prognosis in non-small cell lung carcinomas, renal clear cell carcinoma and colorectal cancer
- Selective NK cell deficiencies are extremely rare
  - Epidemiological study has linked low peripheral blood NK cell activity with increased cancer risk
- Express the transcription factor E4BP4/Nfil3
- 15% of circulating lymphocytes
  - 90% of circulating NK cells are CD56^{dim} CD16^{bright} > ADCC
  - CD56^{bright}CD16^{dim} > secrete Interferon-γ (IFN-γ)
- NK cell subsets can be long-lived and show recall responses to certain stimuli suggesting a role in adaptive immunity

1. Pross HF, Jondal M Clinical and Experimental Immunology. 1975
MODULATING NK CELLS: AN ARRAY OF INHIBITORY AND ACTIVATING RECEPTORS

- Killer-cell immunoglobulin-like (KIR), Human Leukocyte Antigen (HLA)-I

6,000–30,000 different phenotypic NK populations in each healthy individual

What makes NK cells attractive therapeutic targets?

- NK cells have established anti tumor cytotoxicity and cytokine response.
- NK-mediated antitumor effect can be achieved in the absence of graft-vs.-host disease and low cytokine release.
- High number of activating receptors, which provide flexibility to respond to various antigens.
- Participate in the shaping of the adaptive immune response.
Low number of NK cells in peripheral blood and tumor microenvironment

NK cells do not proliferate in vivo

Many patients show down-regulation of NK cell activating receptors

Tumor cells develop immune evasion mechanisms, including down-regulation of the ligands of NK cell activating receptors

Tumor cells are able to acquire NK cell activating receptors in part through lipid structures, which might explain the down-regulation of these receptors in NK cells
MODULATION OF ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

- Approved therapeutic antibodies (such as rituximab or cetuximab) function partially through NK cell-mediated ADCC
- Obinutuzumab (GA101) is a novel type II glycoengineered mAb against CD20 has increased FcγRIII (CD16) binding and ADCC activity.
  - GA101 compared to Rituximab induces activation of NK cells irrespective of their inhibitory KIR expression, and its activity is not negatively affected by KIR/HLA interactions
- Mogamulizumab (an anti-CCR4 mAb) is defucosylated to increase binding by FcγRIIIA (CD16A)
  - Enhances ADCC
  - Approved for CTCL and ATLL
- Anti-KIR Antibody IPH4102 is the first-in-class anti-KIR3DL2 showing activity in CTCL

Mogamulizumab in T-Cell Lymphoma

ATLL

<table>
<thead>
<tr>
<th>Outcome (n=77)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>ORR</td>
<td>33 (43%)</td>
</tr>
<tr>
<td>mOS</td>
<td>7.7 months (5-11)</td>
</tr>
<tr>
<td>3 y. OS</td>
<td>18%</td>
</tr>
</tbody>
</table>


CTCL MAVORIC Trial

Figure 1. Primary Endpoint: Progression-free Survival
- In patients without LCT, ORR is 51.7% and median PFS is 12.9 months
- IPH4102 induces depletion of Sézary/KIR3DL2-positive cells in blood and in skin
- Biomarker of response: KIR3DL2 pre therapy expression and rate of depletion
ADOPTIVE TRANSFER OF AUTOLOGOUS NK CELLS

- Focused on endogenous CD 56 selected NK cells
- IL-2 was administered to provide *in vivo* support for NK cell expansion.
- Limitation:
  - Toxicity: vascular leak syndrome from IL-2 therapy
  - IL-2-induced expansion of regulatory T cells that inhibit NK cell function and induce activation-induced cell death
  - Lack of antitumor effect related to the inhibition of autologous NK cells by self-HLA molecules
- Strategies to overcome this autologous “checkpoint,”
  - anti-KIR Abs to block the interaction of inhibitory receptors on the surface of NK cells with their cognate HLA class I ligand

ADOPTIVE TRANSFER OF ALLOGENEIC NK CELLS

• Taking advantage of the inherent alloreactivity afforded by “missing self”
• Infusion of haploidentical NK cells to exploit KIR/HLA alloreactivity is safe and active in AML
• Phase I study: AML patients who received the more intense Hi-Cy/Flu + Allogenic NK cells were noted to have 5/19 CR
  • Better modulation of T cell-mediated rejection
  • Higher levels of cytokines, such as IL-15
• Ex-vivo methods optimized in the preclinical setting have been successfully scaled up for the clinic
• Other sources of NK- cells
  • Cord blood NK cells
  • Human NK cell lines

CHIMERIC ANTIGEN RECEPTOR-MODIFIED NK CELLS

- CAR-modified NK cells is a field still under development
- Adoptively transferred NK cells have limited in vivo persistence
  - Lack of clonal expansion
  - Immune-mediated rejection of allogenic NK cells
  - Cytokine release syndrome (CRS) less likely
- Opportunity for off-the-shelf allogeneic product
  - Readily available
  - Low concern for GVHD
- Potentially, disease escape through downregulation of the CAR target antigen less likely
  - Intrinsic capacity to recognize and target tumor cells through their native receptors.
- First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia was published
  - Safety in 3 patients

Bispecific NK cell engager: AFM 13

- Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study (Abstract 2908)
- IST – Investigator Sponsored Trial
- Aim: To study NK cell activation in vivo and related immunologic changes as a function of AFM 13 dose and schedule.
  - Evaluation of tumor tissue and peripheral blood histological and biomarker signals as a response to AFM 13 administration.

- >1000x higher affinity for CD16A than monoclonal antibodies
- Binding largely unaffected by competing IgG
- Overcome CD16A polymorphism (V/F)
- No binding to CD16B on neutrophils
# RESPONSE BY COHORT FOR AFM 13 IN CD30 + T- CELL LYMPHOMA

<table>
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<tr>
<th>Cohort</th>
<th>Disease</th>
<th>Toxicity</th>
<th>Response</th>
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<tbody>
<tr>
<td>1.5 mg/m² x 8 weeks</td>
<td>S-ALCL, Alk (-)</td>
<td>No AE</td>
<td>PR</td>
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<tr>
<td></td>
<td>T-MF</td>
<td>No AE</td>
<td>POD</td>
</tr>
<tr>
<td></td>
<td>C- ALCL</td>
<td>Rash (G4) Skin infection (G3)</td>
<td>CR</td>
</tr>
<tr>
<td>7 mg/m² x 8 weeks</td>
<td>MF</td>
<td>IRR (G1)</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>T-MF</td>
<td>IRR (G1)</td>
<td>SD</td>
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<tr>
<td></td>
<td>T-MF</td>
<td>Skin infection (G3) IRR (G1)</td>
<td>Not assessed</td>
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<tr>
<td>7 mg/m² CIVI* x 8 weeks</td>
<td>T-MF</td>
<td>No AE</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>S-ALCL, Alk (-)</td>
<td>No AE</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>No AE</td>
<td>POD</td>
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*1 mg/kg loading 6mg/kg as continuous infusion for 5 days per week
57 year old female with transformed MF

- Previous Therapy
  - NBUVB
  - Romidepsin/Pralatrexate
  - AGS67E (CD37-ADC- MMAE)
- AFM-13: 7 mg/kg CIVI

- Patient achieved Partial Response
- Haploidentical Allogeneic stem cell transplant from son
EVOLUTION OF PATHOLOGY OVER TIME:

<table>
<thead>
<tr>
<th>2015</th>
<th>&gt;</th>
<th>2017</th>
<th>&gt;</th>
<th>2018</th>
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<tr>
<td>CD30</td>
<td></td>
<td>CD30</td>
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<td>CD30</td>
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</table>
CASE STUDY: RESPONSE OVER TIME

Pre Treatment > Cycle 1 Week 8 > Cycle 1 Week 11 > EOS Week 22
CASE STUDY: RESPONSE OVER TIME

Pre Treatment > Cycle 1 Week 8 > Cycle 1 Week 11 > Cycle 2 Week 22
RESPONSE IN LYMPH NODES IN ADDITION TO CUTANEOUS LESIONS: PET CT RESULTS

PRE Study

First Assessment
NK Cells CD56+ CD 3- Decrease On Therapy and Recover Off Therapy

Similar graphs for: NKp46, CD16+CD56+ Expressing Lymphocytes
CD4+ CD25+ CIRCULATING CELLS OVER TIME

**T-regs over time:**
- Decrease @ 1.5mg/kg
- Increase @ 7mg/kg
- Decrease @ 7mg/kg CIVI

**INCREASED STEROIDS USED AT 7MG/KG ARM TO TREAT IRR IS A POSSIBLE CULPRIT**
NK % CD69 Expression In Responders Vs. Non Responders

% CD69 expressing NK cells over time in responders

\[ \Delta +98\% \]

% CD69 expressing NK cells over time in non-responders

\[ \Delta -31\% \]

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Looking Forward

• Combination of immunotherapeutic for synergistic activators of the immune system
  • Check point inhibitors
  • Epigenetic agents
  • Targeted molecules
• Techniques to improve the efficacy of tumor-specific NK cells,
  • Harnessing the innate power of the NK cell
  • Inhibiting or knock out of immune checkpoints
  • Targeting of the tumor microenvironment
• Gene editing techniques being explored in the setting of adoptive T cell therapy
  • CRISPR/Cas9
  • Transcription activator-like effector nuclease (TALEN).
• Off-the-shelf product
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THANK YOU!