NK Cell Immunotherapy: Development of Clinically Effective Strategies to Unleash the Killer within

Adopt summit 2017
London

Lotte Wieten
department of Transplantation Immunology
l.wieten@mumc.nl
The problem…
40% of patients with cancer still die in 2016!

Annual death after failure current cancer treatments
- Metastatic lung cancer: 250,000 (EU)
- Metastatic breast cancer: 90,000 (EU)
- Multiple myeloma: 30,000 (EU)
Cell therapy Maastricht: More cure with less toxicity!

Tumor Immunology

Transplantation Immunology

Clinical hematology

Tissue Typing lab

Maastricht UMC+
Two platforms for Natural killer cell therapy in cancer

Adapted from Vivier Nature Reviews Immunology
Graft versus host and graft versus tumor: A delicate balance requiring HLA matching

- Donor T cells
- NK cells

Healthy Recipient Tissue

Tumor cells

GvHD

GvL

CD8

TCR

HLA

Lysis
Donor selection for HLA-identical allogeneic stemcell transplantation

Parents

Patient

Siblings

no donor

no donor

no donor

donor
Donor selection for haploidentical allogeneic stem cell transplantation

Parents

Patient

Siblings, children, uncles, aunts, nephews and nieces

brother  child  nephew  uncle
Haploidentical bone marrow and immune cell transplantation in breast cancer bearing mice

4T1 (Balb/c) tumor injection (5x10⁴)

donor bone marrow and spleen transplantation

low dose TBI + cyclophosphamide

B6 x Balb/c

CBA x B6

150 days follow-up
Haploidentical bone marrow and immune cell transplantation can cure breast cancer in mice

Syngeneic SPL + BMT (n=40)

CY + TBI+ Transplant
Haploidentical bone marrow and immune cell transplantation can cure breast cancer in mice

CY + TBI+ Transplant

(2 experiments summarized)
Haploidentical bone marrow and immune cell transplantation can cure breast cancer in mice.

- **Haplo SPL + BMT** (n=20)
- **Syngeneic SPL + BMT** (n=40)
- **Haplo “no NK” + BMT** (n=20)

(CY + TBI+ Transplant) (2 experiments summarized)
Haploidentical bone marrow and immune cell transplantation can cure breast cancer in mice.

Sorted Haplo NK + BMT (n=20)
Haplo SPL + BMT (n=20)
Syngeneic SPL + BMT (n=40)
Haplo “no NK” + BMT (n=20)

CY + TBI+ Transplant
Haploidentical donor NK cells are sufficient to cure breast cancer bearing mice

![Graph showing tumor-free survival (%) over time (days) for different treatment groups.](image)

- Haplo NK + Bone marrow cells
- Only Haplo NK cells
- Syngeneic NK cells

NK cell infusion

**Maastricht UMC+**
Natural killer cell alloreactivity upon Haplo-SCT

Ruggeri et al. Science 2002
Vivier, Nature reviews Immunology
Chemo/radiotherapy and alloreactive NK cells delay multiple myeloma progression

Sarkar *et al,* J. Molecular Cytotherapy 2015
Combination therapy to enhance NK cell function in a suppressive tumor microenvironment.
Hypoxia inhibits NK cells
NK cell activation helps to overcome the inhibitory effects of hypoxia}

** NK cells + Dil-labeled tumor cells → Flowcytometry → Dead tumor cells **

** IL-2 - + - + **

** % Specific cytotoxicity **

** Normoxia **

** hypoxia **

*Sarkar et al Plos One 2013*
But… activation alone is not enough to overcome a more suppressive tumor microenvironment.
ADCC triggering antibodies enhance NK cell function in a suppressive tumor microenvironment
Selection of KIR ligand mismatched NK cell donors to improve anti-tumor responses

Comparable results for other combinations of environmental factors
Two platforms for Natural killer cell therapy in cancer

Adapted from Vivier Nature Reviews Immunology
Multicenter study haploidentical stem cell transplantation in Multiple Myeloma patients

- Non-randomized Phase 2 study
- Selection of KIR-ligand mismatched donors

Objectives:
- Progression free survival
- Engraftment, GvHD, infections
- Non-Relapse Mortality
- T cell and NK reconstitution
- NK cell repertoire
- Cost calculation
- Quality of Life
NK cell reconstitution upon HaploSCT

Combination therapy: HaploSCT, NK infusion and antibodies and/or immunomodulatory agents
Ex vivo expansion of GMP-grade NK cells

- Donor
- Patient with cancer

Leukopheresis

NK cell isolation

infusion
Ex vivo NK cell expansion

3-6 x 10^9 cells
Ex vivo expanded NK cells express the required receptor repertoire
Valorisation of adoptive NK cell therapy

Optimization bioreactor protocol
Target >10 x 10^{10} cells

Clinical trials:
Multiple Myeloma (n = 30)
Breast cancer (n = 30)
+ controls (n = 60)
Maastricht cell-based Immunotherapy: aiming at cure with low off target toxicity

Platforms for NK based immunotherapy:

*Haploidentical Stem cell transplantation*
  - Clinical multicenter study,
  - Ongoing studies to improve donor selection and therapeutic protocols

*Adoptive NK cell therapy*
  - Expansion of GMP-grade NK cells
  - Valorisation in collaboration with industry
  - Studies to improve NK cell function are ongoing

*Combination therapy*