Immunotransplant for Mantle Cell Lymphoma: A phase I/II study demonstrating amplification of tumor-reactive T cells

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Presenter Disclosure Information

Joshua Brody M.D.

The following relationships exist related to this presentation:

<No Relationships to Disclose>
in situ vaccine
(low grade lymphoma)

autologous transplant
(mantle cell lymphoma)
CpG-based vaccine for *low-grade* lymphoma

Brody JD et al., *J Clin Oncol.* 2010 Oct 1;28(28).
CpG-based vaccine induces anti-tumor T cells

Brody JD et al., J Clin Oncol. 2010 Oct 1;28(28).
T-cell transfer into lymphodepleted recipients induces preferential $T_{\text{effector}} > T_{\text{reg}}$ proliferation.
Immunotransplant amplifies anti-tumor T cells induced by CpG-based vaccines

**CpG in situ vaccine**
- CpG
- NHL vaccinated donor
- T cells
- Lymphodepleted recipient
- CD44

**CpG ex vivo vaccine**
- CpG-NHL
- Transplant

Brody JD, et al., *Blood*. 2009 Jan 1;113(1).
Immunotransplant for MCL: schema & endpoints

Primary endpoint: immune response
- IFNγ
- TNF
- IL2
- perforin
- granzyme

MCL

CpG

Vaccine

Vaccine-primed T cells

Autologous transplant

Immunotransplant

Induction chemotherapy

Biopsy

CD137

Tumor-reactive T cell
## Immunotransplant for MCL: cohort

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CpG-MCL vaccine: CpG differentially induces activation markers

media

CpG

CD80

CD86

isotype-P

CD40

HLA-ABC

HLA-DR

isotype-A

isotype-F

fold-change with CpG

CD25 CD40 CD54 CD69 CD70 CD80 HLA-ABC HLA-DR %CD3
Immunotransplant for MCL: immune response
Induction of tumor-reactive T cells occurs only after immunotransplant

CD8 T cells

- **Pre-vaccine**
  - CD45RO: 6.9%
  - granzyme B: 1.8%
  - perforin: 1.8%

- **Post-vaccine**
  - CD45RO: 9.6%
  - granzyme B: 2.7%
  - perforin: 2.7%

- **Post immunotransplant**
  - CD45RO: 25.6%
  - granzyme B: 10.6%
  - perforin: 10.6%
Immunotransplant for MCL: immune response

Induction of tumor-reactive T cells occurs only after immunotransplant.

Graph showing the percentage of tumor-reactive T cells (vs baseline) post-vaccine for different patients and cell types.
Immunotransplant for MCL: immune response
Induction of tumor-reactive T cells occurs only after immunotransplant

% tumor-reactive T cells (vs baseline)

CD4 cells  CD8 cells

post-immunotransplant

0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0

patient #

0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0

CD137  IFNg  TNF α/β  IL-2  CD137  IFNg  TNF α/β  IL-2  perforin  granzyme B
Immunotransplant for MCL: preliminary results

A proportion of tumor-

reactive

T cells are tumor-
specific

CD8 T cells

pre-vaccine

post-vaccine

post immuno-

transplant

2.8%

4.5%

31.4%

2.8%

3.8%

21.2%

T cell

MCL

B cells

tumor

grazyme

normal

B cells

tumor

B cells

ggranzyme

T cell

CD45RO

grazyme

B
Tracking T cells with TCRβV high throughput sequencing: few T cell clones are amplified by CpG-MCL vaccine
Tracking T cells with TCRβV high throughput sequencing: more T cell clones are amplified by immunotransplant.
Tracking T cells with TCRβV high throughput sequencing: some T cell clones are amplified by *in vitro* tumor co-culture
TCRβV high throughput sequencing

tumor-reactive T cells are amplified by immunotransplant

In vitro tumor co-culture (log fold-change)

p < 0.001

fold-change by immunotransplant

(all T cells)

100x vitro-amp

1000x vitro amp

(log-fold change)
Future Directions:

1) Assess whether immunotransplant improves the molecular remission rate compared to recent large studies of standard transplant for MCL:

2) Immunotransplant for:
   - aggressive NHL, PTCL, Myeloma

3) Non-ablative immunotransplant (e.g. fludarabine-based) for:
   - Hematologic: low-grade NHL, elderly MCL
   - Solid tumor: prostate CA
   melanoma
Thanks:

Lympoma Team:
Ranjana Advani
Holbrook Kohrt

Transplant Team:
Robert Negrin
Kevin Sheehan
BMT Lab

Immune Studies
Debra Czerwinski
Etelka Gabriel

Biostatistics
Phil Lavori

Funding:
Lymphoma Research Foundation
NCI K99/R00 ‘Pathway’ Award

Mentorship:
Ronald Levy
Shoshana Levy

High Throughput Sequencing
Malek Faham
Victoria Carlton
(Sequenta Inc.)

PF-3512676
Pfizer Inc.

All of the patients on:
NCT00185965
NCT00880581
NCT00490529
extra
**T$_{reg}$-inducing tumors: inverse correlation with outcome**

**gated on CD4 T cells**

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**Progression Free Probability**

- T$_{reg}$ Inducers: $p = 0.0058$
- T$_{reg}$ Non-Inducers