Brain Tumor Immunotherapy

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Conflicts of Interests:
Hideho Okada, MD, PhD is an inventor of the IL-13Rα2 (345-353:1A9V) peptide, for which an exclusive licensing agreement has been executed with Stemline, Inc.
Per COI policies, interpretation of presented data was not performed solely by Hideho Okada, but by the investigator team.
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Voices Against Brain Cancer
Participants and their families
Genetic pathways to primary and secondary glioblastomas


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Immunotherapy approaches that are currently evaluated in glioblastoma

- **Vaccine** – dendritic cell (DC)s loaded with lysate, peptides targeting epitopes, such as EGFRviii, cocktail of 10 non-mutated antigens (IMA950), CMV etc.

- **T-cell Adoptive transfer** - CAR targeting EGFRviii, IL-13Ra2, Her2 etc.

- **Immune checkpoint inhibitor** - blockade of TGF-beta, anti-PD-1 plus anti-CLTA4, anti-PD-L1

- **Oncolytic virus** - oncolytic HSV expressing IL-12
Is the brain immune privileged (or not)?

The concept originated in 1921 in Japan, when Shirai observed that rat sarcoma cells grew well when transplanted into the mouse brain parenchyma, but were rejected when implanted subcutaneously or intramuscularly.

**Immune privilege is:**
- Relative
- Confined to central nervous system (CNS) parenchyma (see below)
- Characterized by lack of the afferent arm in adaptive immunity

**Immune privilege is not:**
- Absolute
- Solely attributed to the blood–brain barrier (BBB)
- Present in meninges, choroid plexus and ventricles
- Preserved as observed as neurotoxicity in recent cancer immunotherapy studies
- Preserved in the inflamed CNS

_Galea I et al. Trends in Immuno 2007_
_Ransohoff RM and Engelhardt B. Nat. Rev Immuol 2012_
What is “Immuno-Privilege”?

CNS Immune Arc | Peripheral Immune Arc

+++ | +++
- | +++
+ or ++ | +++

Cervical or inguinal lymph node

+++ Afferent Arm: soluble Ags
+++ Afferent Arm: cellular route (DCs)
+++ Efferent Arm: leukocytes and Abs

Ian Galea et al. Trends in Immunol 2007 with modifications
Central Nervous System (CNS) immunology
- Missing Afferent but somewhat functional Efferent Arms-

• Autoimmune diseases in the CNS (Experimental Autoimmune Encephalitis, Multiple Sclerosis, Paraneoplastic Cerebellar Degeneration [PCD] against cdr2)
  - Patients with undiagnosed cancers (e.g. ovarian cancer) visit neurologists’ office complaining ataxia (cerebellar signs)
Discussion with Dr. Paul Walker  
(University of Geneva)

• The lack of afferent arm is relative, too (not absolute).

• Evidence for glioma antigen-specific T cells in TILs of untreated patients (e.g. high frequency of T cells specific for the BCA_{478–486} peptide; Dutoit V et al. Brain 2012).

• Spontaneous anti-glioma immunity is delayed because the threshold for stimulating the afferent arm is high – and we do get a spontaneous immune response when this threshold is reached.
Critical factors mediating efficient CNS-tumor homing of T cells

  
  – Anti-VLA4 mAb Natalizumab in MS patients caused progressive multifocal leukoencephalopathy (PML) by re-activation of JC virus, suggesting T-cell immunosurveillance

Up-regulated expression of CXCL10 mRNA in murine GL261 glioma treated with glioma-associated antigen (GAA)-vaccines and i.m. poly-ICLC (*In situ* hybridization)

A Vaccine Plus Poly-ICLC  B Vaccine Alone

C Poly-ICLC Alone  D Mock-Treatment

Fujita M. *et al.* Cancer Res. 2011
Poly-ICLC administration enhances the infiltration of antigen-specific T cells and therapeutic efficacy.

Brain-Infiltrating T-cells

These cells express “brain-homing” receptors VLA-4 and CXCR3

Anti-Tumor Effect

Zhu X. Okada H et al. 2010
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Setting</th>
<th>Patient population</th>
<th>Vaccine Type</th>
<th>Antigens</th>
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<th>Funding Sources</th>
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<td>Dendritic cells</td>
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“Immuno-Prevention” in WHO Grade II Low-Grade Glioma (LGG) Patients?

– Slow-growing (compared with Grade III or IV), but non-curable
– Tends to occur in young adults and prognosis 3 to 10+ years; More than 50% of LGG transform to High-Grade Gliomas (HGG)
– Radiation (RT) or chemotherapy not curable – Doctors often take “careful follow-up” without any active treatment – Life with a “timed bomb”
– Robust induction of type-1 T-cell response and preliminary clinical response in both adult and pediatric HGG patients in our previous phase I/II studies (Okada H. et al. JCO 2011; Pollack IF et al. JCO 2014)
– LGG patients may not be as immuno-suppressed as HGG patients and the slow growth rate of LGG should allow sufficient time to repeat multiple vaccinations

– Can vaccination in these patients prevent progression and recurrence? - prophylactic brain cancer vaccine?
Synthetic glioma-associated antigen (GAA) peptides and heterologous helper antigens used in the vaccine

<table>
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<th>Antigen Peptide</th>
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<th>Prevalence in HG / GIIA</th>
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<td>IL-13Rα2 345-353:1A9V</td>
<td>HLA-A2</td>
<td>&gt;80% / low</td>
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<tr>
<td>EphA2 883-891</td>
<td>HLA-A2</td>
<td>75-80%/ 50%</td>
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<td>Survivin 96–104:M2</td>
<td>HLA-A2</td>
<td>All astrocytoma (GII-IV)</td>
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<tr>
<td>WT1 126-134:Y1</td>
<td>HLA-A2</td>
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Tetanus Toxoid (Tet<sub>A830</sub>) Pan-DR

HG; high grade (grade III-IV) glioma, GIIA; grade II astrocytoma

- The vaccine was formulated as the mixture of these peptides (300 mcg/peptide) in Montanide ISA-51 for subcutaneous administration every 3 weeks x 8 times
- Poly-ICLC (20 mcg/kg) was administered intramuscularly on the day and on day 4 following each vaccine

Primary Objectives are to determine safety and glioma-associated antigen (GAA)-specific immune responses of the regimen.

Three Cohorts  All cohorts enrolled HLA-A2+ adult WHO G2 LGG

Cohorts 1 and 2- WHO grade II astrocytoma or oligoastrocytoma with “high-risk” factors – at least one of the following conditions: 1) age ≥ 40; 2) incomplete resection or 3) the tumor size is ≥ 4 cm

Cohort 3 – recurrent WHO grade II gliomas
IFN-γ ELISPOT assays on each of vaccine-targeted antigens in Cohorts 1 and 3

Cohort 1 (Newly Dx)
- IL-13Rα2
- EphA2
- WT1
- Survivn
- Tetanus

Cohort 3 (Recurrent)

Weeks post First Vaccine (“B” for Boosters)

0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24 0 18 24

Mean

Spots/10^5 cells

11/22/2014

Transient Appearance of Gd Enhancement in a Pt with WHO grade II Oligodendroglioma (IDH1 mut+) Receiving Vaccine

12/23/13 (30d post 2\textsuperscript{nd} Vac) 1/14/14 (11d post 3\textsuperscript{rd} vac) 1/22/14 (19d post 3\textsuperscript{rd} vac)

T2 Flair

T1-Gd (two consecutive slices)

The ESMO Symposium on Immuno-oncology 2014
Summary from the pilot LGG vaccine study

• No regimen-limiting toxicity was encountered except for one case with Grade 3 fever and fatigue (Cohort 1).

• **Newly diagnosed** (Cohort 1) patients demonstrated significantly higher IFN-γ responses than **recurrent** (Cohort 3) patients and **pediatric** glioma patients receiving the same vaccine (Pollack IF Okada H et al. J. Clin Onc. 2014)

• For clinical benefit evaluation, **pseudo-progression on MRI may hamper proper PFS evaluation.** We also reported this issue multiple times (Okada H. et al. JCO 2011, Okada and Pollack 2012, Pollack IF et al. 2014)

• Nonetheless, these data support further development of the approach with further refinement of target antigens etc.
Overall Summary and Directions

• Understanding of central nervous system (CNS) immunology and CNS tumors is essential for developing novel immunotherapy strategies for CNS tumors (although I did not present),

• Combination of novel technologies, such as CAR and checkpoint inhibitors, need to be investigated

• Personalized vaccines based on novel technologies, such as NGS, are being developed

• A phase II study for low-grade glioma vaccine is being developed as a concept

I am stopping my talk

- We will continue our collaboration!
The Cancer-Immunity Cycle (Chen and Mellman, Immunity 2013)
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle
(Chen and Mellman, Immunity 2013)
Robust Induction of GAA–Specific, poly functional CD8+ cell Response in a Subject with WHO Grade 2 Low Grade Glioma

% of EphA2 tetramer+ cells in CD8+ cells
% of IL13Ra2 tetramer+ cells in CD8+ cells
% of Survivin tetramer+ cells in CD8+ cells
% of WT1 tetramer+ cells in CD8+ cells

Pre-Vaccine | WK12 | WK18 | WK24
---|---|---|---
WT1 | 0.019 | 0.772 | 5.63 | 5.99
SSC

Tetramer+ Gated Cells
CD27
CD45RA


11/22/2014
The ESMO Symposium on Immuno-oncology 2014
Immunosuppression among glioblastoma patients is mediated by systemic and local (microenvironment) factors

1. Decreased T-cell responsiveness
2. Increased circulating Tregs (CD4+/CD25+/FoxP3+)
3. Diminished IgG production

Systemic Immunosuppression

Local (microenvironment) Immunosuppression

1. Downregulation MHC molecules
2. Increased infiltrating Tregs (CD4+/CD25+/FoxP3+)
3. Hypoxia mediated impaired T cell function
4. Secretion of immunoinhibitory cytokines (TGF-β, VEGF, IL-10, prostaglandin E2, LLT-1)
5. Immunosuppressive microglia/TAM (up to 40% GBM mass!)
6. GBM expression of Fas ligand (apoptosis of activated T cells)
7. Increased expression PD-L1

Reardon D et al. 2013

The ESMO Symposium on Immuno-oncology 2014
• **Primary Brain Tumor**
  - Tumors that originate in the CNS
  - Approx. 40,000 pts/year in the USA
  - e.g. gliomas (WHO grade 1-4) and meningiomas

• **Metastatic Brain Tumor**
  - Most common primary sites are lung, breast, kidney and melanoma
  - Approx. 170,000 pts/year in the USA
  - 20-25% of all cancer
  - As our ability to diagnose and treat primary tumors improves, a shift in mortality towards metastatic disease has been observed.

On MRI, contrast agents such as gadolinium can inform us about CNS pathology only when the BBB has been compromised.
Distribution of Primary Brain and Central Nervous System (CNS) Tumors by Histology (N = 311,202)

Glia (ICD-O-3: 9380-9384, 9391-9460, 9480) account for 29% of all tumors and 80% of malignant tumors.

Dolecek T A et al. Neuro Oncol 2012;14:v1-v49