Assess Response to Immunotherapy with Magnetic Resonance Imaging in Brain Gliomas

Brisbane, September 4th

Alberto Bizzi, M.D.
Outline

Immunotherapy in GBM
- Principles of immunotherapy in cancer
- Immunotherapy strategies for GBM
- Clinical issues and solutions

Assessment of therapy response with MR imaging
- True progression vs. Pseudoprogression
- Limitations of Gadolinium enhancement
- RANO (Response Assessment Neuro-Oncology) criteria
- Expanded time window with immunotherapy (iRANO)

Assessment of response with advanced MRI methods
- TRAMs may separate active tumor from inflammatory response
- High rCBV suggests tumor with angiogenesis
- Low diffusivity (ADC) suggests high cell density (tumor and inflammatory reaction)
- Increasing Cho signal by H-MRSI suggests tumor progression
Principles of Immunotherapy

- Immune cells can cross the blood-brain barrier (BBB) to gain access to the brain parenchyma and can leave the CNS to reach the cervical lymph nodes.
- GBMs express multiple tumor antigens that can be targeted by immunotherapy.
- Cancer epitopes are recognized by the immune system, thus an immune reaction can be mounted to erase or block tumor growth.
- Resistant tumor clones, grown under immune pressure, create an immune suppressive environment that leads to the formation of relevant tumor.

Cancer immunotherapy strategies are aimed at reverting such immune suppression.
The 3 phases of the cancer-immunoediting process

**Transformed**
- MICA/B ULBP (Human)
- Rae-1
- H60 (Mouse)

"Danger": uric acid, ECM products

**Elimination** (Cancer Immunosurveillance)
- Innate & Adaptive Immunity
- IFNγ, Perforin, TRAIL

**Equilibrium**
- Genetic instability/immune selection

**Escape**
- CD8⁺
- CD4⁺CD25⁺ Treg
- Galectin-1
- IDO
- sMICA/B

E.g., ↓p53, ↓Rb, ↑Ras
- Carcinogens
- Radiation
- Chronic inflammation
- Inherited
- Viruses

Dunn, Old and Schreiber, Immunity 2004
Novel immunotherapeutic strategies

In GBMs 3 major classes of treatments are being currently investigated:

① Active vaccination therapy
   - Peptide immunotherapy where the target is a cancer-specific antigen like EGFR vIII
   - Dendritic cell immunotherapy (dendritic cells act as antigen-presenting cells)

② Adoptive cellular immunotherapy with cytotoxic T lymphocytes

③ Immunomodulatory strategies
   - Checkpoint inhibitors facilitate effective antitumoral immune response as they suppress the tumor-mediated inhibition of the immune system
Glioblastoma immunotherapy strategies

Immunotherapy is the process by which the host immune system is modulated in an attempt to generate a tumor-targeted response

①Adoptive cell therapy (ACT) whereby the host immune system is stimulated to elicit a response

②Immunovirotherapy which involves the use of oncolytic viruses which are only capable of replication within cancer cells with subsequent cell lysis

③Peptide vaccinations are developed through either tumor isolated, or synthesized, peptide fragment which, when combined with carrier protein adjuvants, are then used to vaccinate the host against a particular antigen

④Dendritic-cell vaccination whereby tumor specific antigens (TSA) and tumor associated antigens (TAA),s are used to direct a dendritic cell-prompted immune response
GBM immunotherapeutic strategies

Oncotarget 2014; 5(24): 12472-12508
The cancer-immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)

APCs: Antigen Presenting Cells

Chen and Mellman, Immunity 2013
GBM are very heterogeneous neoplasms, thus *multiple treatment strategies of immunotherapy* in addition with conventional radiochemotherapy (Stupp protocol) will be more likely to succeed.

Preliminary data have shown prolonged overall survival in GBM treated with vaccines: *an increase from 23 to 38 months* (Xu LW et al. - J of Immunology Research 2014).

Results in upcoming clinical trials will clarify the efficacy of novel cancer immunotherapy strategies, in particular using *dendritic cell vaccines and checkpoint inhibitors* (anti-PD-1 antibody, i.e. *Nivolumab*).
Clinical issues during immunotherapy

Efficacy of therapy is assessed by clinical examination and MR imaging

1. True early progression
2. Pseudoprogression
3. Vasogenic edema
4. Seizure control
<table>
<thead>
<tr>
<th>Critical clinical problems</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>True early progression</td>
<td>Stop therapy</td>
</tr>
<tr>
<td><strong>Pseudoprogression</strong></td>
<td><strong>Continue therapy</strong></td>
</tr>
<tr>
<td>Extensive vasogenic edema</td>
<td>Use mannitol rather than steroids that would suppress the immune response</td>
</tr>
<tr>
<td>Seizures control</td>
<td>Reduce edema and inflammatory response</td>
</tr>
</tbody>
</table>
Pseudoprogression in glioblastoma (GBM)

3 months post radiotherapy

Stable

No additional therapy at 6 months
Pseudoprogression: definition

- An increase in contrast enhancement with or without edema during or immediately after the end of treatment in a clinically stable patient
- Lesions decrease in size or become stable by continuation of previous treatment or without additional treatment
- It is a treatment effect (i.e. inflammatory reaction, increased permeability) due to:
  1. Radiotherapy alone
  2. RT plus temozolamide in up to 50% GBM with MGMT+
  3. Immunotherapy
Response Assessment in Neuro-Oncology

- MRI is the main imaging modality

- Minimal imaging protocol required:
  - Pre-contrast T1w and T2-FLAIR
  - Post-contrast 3D-T1w (or 2D with two orthogonal planes)
  - ≤5 mm slice thickness with no gap is recommended

- Advanced imaging methods may be helpful to better characterize the microscopic tissue, however interpretation is not straightforward:
  - TRAMs (Therapy Response Assessment Maps)
  - Perfusion (DSC, DCE, pCASL)
  - Diffusion (DWI, ADC)
  - MR Spectroscopy (H-MRS)

- FET- and MET-Positron Emission Tomography results are also promising

New criteria were proposed in 2010

<table>
<thead>
<tr>
<th>Criterion</th>
<th>True disease response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 with Gd</td>
<td>Gone</td>
<td>&gt;50% decreased Δ</td>
<td>&lt;50% decreased Δ</td>
<td>&gt;25% increased Δ</td>
</tr>
<tr>
<td>T2WI/FLAIR</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Declined</td>
</tr>
<tr>
<td>Requirements for response</td>
<td>All of above</td>
<td>All of above</td>
<td>All of above</td>
<td>Any of above</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Outcome</th>
<th>Agent</th>
<th>Enhancement</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoresponse</td>
<td>Bevacizumab</td>
<td>Decreased</td>
<td>~ 2-4 days</td>
</tr>
<tr>
<td>Pseudoprogression</td>
<td>Radiation with Temozolamide</td>
<td>Increased</td>
<td>~ 3-4 weeks, less than 6 mos.</td>
</tr>
<tr>
<td>True disease response</td>
<td>any</td>
<td>Decreased</td>
<td>&gt; 3 months</td>
</tr>
<tr>
<td>True tumor progression</td>
<td>any</td>
<td>Increased</td>
<td>&gt; 3 months</td>
</tr>
<tr>
<td>Delayed radiation necrosis</td>
<td>Radiation</td>
<td>Increased</td>
<td>Longer than 6-12 months</td>
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Gadolinium enhancement does not answer the question

*Time of assessment is a key factor*
Immunotherapy Response Assessment in Neuro-Oncology (iRANO): A Report of the RANO Working Group

Hideho Okada, MD¹, Michael Weller, MD², Raymond Huang, MD³, Gaetano Finocchiaro, MD⁴, Mark R. Gilbert, MD⁵, Wolfgang Wick, MD⁶, Benjamin M. Ellingson, PhD⁷, Naoya Hashimoto, MD⁸, Ian F. Pollack, MD⁹, Alba A. Brandes, MD¹⁰, Enrico Franceschi, MD¹⁰, Christel Herold-Mende, PhD¹¹, Lakshmi Nayak, MD¹², Ashok Panigrahy, MD¹³, Whitney B. Pope, MD¹⁴, Robert Prins, PhD¹⁵, John H. Sampson, MD¹⁶, Patrick Y. Wen, MD¹², and David A. Reardon, MD¹²
### iRANO criteria

Okada H et al - Lancet Oncology 2015

- It may take time for immunotherapy to kick in
- Residual tumor may progress during this time frame
- The “limbo window” is extended to 6 months if the pt is stable

<table>
<thead>
<tr>
<th>Neuro exam</th>
<th>Clinically stable (SD)</th>
<th>Clinical decline (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timeline</td>
<td>&lt; 6 mos</td>
<td>&gt; 6 mos</td>
</tr>
<tr>
<td>Is a repeat scan required to confirm PD?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is further immunotherapy allowed after initial radiographic progression pending progression confirmation?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Does a new lesion define PD?</td>
<td>No</td>
<td></td>
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57 F presenting with dysarthria and dysphasia

GBM WHO-IV
MGMT methylated, p53, PTEN
IDH-wt, EGFR e EGFR vIII pos

T2WI

T1Gd

Courtesy of Valeria Cuccarini
3 months after 1st surgery and after STUPP, immediately before immunotherapy

Trial DENDR 1 (dendritic cells)
Immunotherapy if residual Gd+ tumor is < 10cc
Recruitment is done before starting STUPP
2 months following immunotherapy
4 months following immunotherapy
7 months following immunotherapy
12 months following immunotherapy

Courtesy of Valeria Cuccarini
Pseudoprogression after immunotherapy

- The precise mechanism is unknown
- In a few biopsied cases histopathology showed infiltration of CD8+ lymphocytes, but not mitotically active tumor cells
- Effective immune response might need time to evolve, and early imaging might reflect true progression
- Inflammatory response in areas of macroscopic or microscopic infiltrative tumor might mimic tumor progression with increased enhancement, edema, permeability, lipids (natural killer T-cells) and decreased ADC
- Patients with enlarging or new lesions should repeat the MRI 4 weeks later
The lesional maximum rCBV and minimum ADC values in the contrast-enhancing area are potential radiological markers to differentiate between immunotherapy-induced inflammatory response and recurrent tumour growth in glioblastoma patients treated with dendritic cell vaccine.
Cerebral Blood Volume (CBV) in stable disease

T1WI post-Gad

$T_0$, 1 month, 4.5 mos, 9 mos, 15 mos

Vrabec V, Van Cauter S, Sunaert S et al - Neuroradiology 2011
CBV in progressive disease

T1WI post-Gad

$T_0$, 6 weeks, 4.5 mos, 7.5 mos, 10.5 mos

Vrabec V, Van Cauter S, Sunaert S et al - Neuroradiology 2011
Three of the eight patients progressed during the study period. The time from the start of immunotherapy to progression was from 7 to 40 months (median 7.5 months). The remaining five patients remained stable clinically as well as radiologically until the end of the study (10–44 months; median 15 months).
Immunotherapy with dendritic cells vaccine

Mismatch

T1-enhancing tumor with relatively low CBV

Elevated $k_{\text{trans}}$ and low ADC are not specific

$K_{\text{trans}}$ (permeability)
Preliminary results

◇ 22 pts with GBM at 1st diagnosis treated with dendritic cell immunotherapy after Stupp enrolled in the EUDRACT trial
◇ 10 received benefit from treatment (respondent) based on PFS >12 mos and 12 have not
◇ A decrease in rADCmean >0.13 was a significant predictor of longer PFS
◇ During the follow-up 7 pts experienced pseudoprogression and 18 pts eventually had progression. A significant increase of rCBV and decrease of rADCmean were observed only in pts with true tumor progression. A rCBV threshold of 2.07 was able to distinguish the two conditions with a sensitivity of 100% and specificity of 60% (p=0.004)

1) An early decrease in rADC was related to better survival in GBM: this finding underlines the relevance of hypercellularity in the 1st phase of the immunotreatment
2) Modification of rCBV can be useful in distinguishing progression from pseudoprogression
**H-MRSL during immunotherapy**

True progression after surgery and Stupp

Pseudoprogression @ 3 mos after surgery and start of immunotherapy with dendritici cell vaccine

Mixed scenario
*Delayed* radionecrosis with signs of true progression
Treatment Response Assessment Maps (TRAMs)

- Acquisition: delayed post-gadolinium 3D T1-weighted sequences at 3-5 and 60-75 min after the injection of contrast agent
- Post-processing includes subtraction of early from late sequence
- Color-coded maps to differently represent areas in which contrast accumulates during time (red-coded) and regions in which it is rapidly cleared from the tissue (blue-coded)
- Histological validation confirmed signs of inflammatory response in red areas and active tumor in blue areas
Treatment Response Assessment Maps (TRAMs)

A: T1WI post-Gad
B: TRAM
C: rCBV

NSCLC metastases

Zach L - Neuro-Oncology 2015
Treatment Response Assessment Maps (TRAMs)

T1WI post-Gad

TRAMs

rCBV

High

Moderate

Low rCBV

GBM

GBM

Melanoma

Zach L - Neuro-Oncology 2015
Treatment Response Assessment Maps (TRAMs)

T1WI post-Gad

TRAMs post-chemioradiation

3 weeks  10 weeks  4 mos  6 mos
Take home points

✧ Do not overinterpret the MRI findings without an accurate and complete therapy history
✧ **Pseudoprogression** does not affect management: treatment is maintained if the patient remains clinically stable

★ Advanced MR imaging should help:
  o **DWI/ADC** valuable in evaluating pseudoresponse
  o **rCBV** and **H-MRSI** are very valuable to evaluate questionable cases of pseudoprogression
  o **TRAMs** are user-independent and have the potential to separate active tumor from inflammatory response

★ Advise to repeat the MR every two months
Collaborators

Elena Anghileri, M.D.
Domenico Aquino, B.E.
Maria Grazia Bruzzone, M.D.
Valeria Cuccarini, M.D.
Marica Eoli, M.D.
Gaetano Finocchiaro, M.D.