Immunotherapy for the Treatment of Brain Metastases

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Advances in Cancer Immunotherapy™
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Slides from Annie W. Silk, MD from Rutgers Cancer Institute of New Jersey
Disclosure

Receipt of Intellectual Property Rights/Patent Holder
- Trans Target, Inc.

Contracted Research
- Dendreon
- Millenium
- Pharmacyclics

Ownership Interest
- Seattle Genetics
Outline

1. Background
2. Immune surveillance and response in the CNS
3. Clinical experience with immunotherapy for the treatment of brain metastases
4. Rationale for combination therapies
Brain Metastases (BM)

- 20-40% of cancer patients will develop BM
  - Lung (50%)
  - Breast (15%)
  - Melanoma (50-65%)
- The incidence of BM is increasing
  - HER2-positive breast cancer (30-55%)
  - ALK mutated NSCLC
Radiation Therapy is the Backbone of Treatment

<table>
<thead>
<tr>
<th>One BM</th>
<th>A few BM</th>
<th>Numerous BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Stereotactic radiosurgery (SRS)</td>
<td>Whole Brain Radiotherapy (WBRT)</td>
</tr>
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</table>
Limits of cytotoxic and targeted therapy

Levels of most cytotoxic and targeted drugs in brain metastases is a fraction of level in blood due to the blood brain barrier
CSF drains to blood and lymph

- CSF drains from the subarachnoid space
  - To venous blood
  - To lymph

- Antigen presenting cells in the **deep cervical lymph nodes** can recognize soluble antigens in the CSF

- APCs in the **deep cervical lymph nodes** prime T cells → adaptive immunity

Outline

1. Background
2. The Blood Brain Barrier (BBB)
3. Immune surveillance and response in the CNS
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5. Rationale for combination therapies
Is the brain a sanctuary?

- The brain contains no lymph nodes.
- The parenchyma of the brain does not have conventional antigen presenting cells.
Evidence for immune privilege

1. In experimental models, antigens such as tumor cells, viruses, bacteria that are placed inside the brain parenchyma will **not** trigger a cell-mediated immune response.

2. Peripheral immunization with an intra-parenchymal self antigen will trigger a brisk and robust immune response.

Clearly immune privilege in the brain is not absolute

- T-cells can cross the BBB
  - In health
    - Surveillance
  - In response to pathogens and cancer
    - Infectious meningitis and encephalitis
    - Brain metastases
  - In autoimmune disease
    - Multiple sclerosis
    - Ipilimumab-related hypophysitis
Memory T cells are responsible for immune surveillance in CNS

- T cells enter the CNS through the subarachnoid space (SAS)
- APCs in SAS can re-prime the T cells → inflammation

Immune infiltrate in BM and more favorable survival

- Resected brain metastases of patients with melanoma
- Peritumoral CD3+ and CD8+ cells were associated with prolonged survival

Hamilton et al 2013 Cancer

CD8+ T cells (blue)
Immune infiltrate in BM and more favorable survival

- Immunostaining study of 287 brain tumors
  - 170 BM (77 Lung, 44 Melanoma, 22 Others, 10 Renal)
  - 117 glioblastoma multiforme (GBM)

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<tr>
<th></th>
<th>BM</th>
<th>GBM</th>
<th>p</th>
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<tr>
<td>Dense CD3+ TILs</td>
<td>+++</td>
<td>+</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Dense CD8+ TILs</td>
<td>+++</td>
<td>+</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Dense PD-1+ TILs</td>
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- Dense CD3+ tumor infiltrating lymphocytes (TILs) correlated with more favorable survival in BM patients (12 vs. 9 months; p = 0.015)
- Suggests that immunotherapy may be a viable strategy for BM
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Interleukin-2 for BM

- IL-2 has not been used extensively in patients with untreated BM due to the risk of cerebral edema.

- Patients with stable previously irradiated or asymptomatic BM do not appear to have excess toxicity with IL-2 therapy.

- The response rate in previously untreated brain metastases was 5.6% in one series.

- Complete responses in the CNS have been reported.

Guirguis, et al 2002
Powell and Dudek, 2009
Activity of Ipilimumab in BM in 51 neurologically asymptomatic pts

- Phase II in 72 patients with BM
- n=51 were neurologically asymptomatic, n=21 were neurologically symptomatic
- 40% had received previous radiation therapy (wash-out period 2 weeks)

- Treated with ipilimumab 10 mg/kg IV Q3 weeks x 4, followed by Q12 week maintenance
- Response was assessed after 12 weeks using modified WHO and immune related response criteria
- Previously irradiated brain lesions could not be index lesions unless they were progressive despite radiation therapy

Margolin, et al 2012 Lancet Oncol
Activity of Ipilimumab in BM

- Response rate in the CNS
  - 16% in asymptomatic subjects
  - 5% in symptomatic subjects
    - 1 CR, 0 PR
- 2 year overall survival ~25% in the asymptomatic subjects

Margolin, et al 2012 Lancet Oncol
Ipilimumab + Fotemustine

- Fotemustine can cross the BBB
- 86 patients with metastatic melanoma were treated with ipi + fotemustine
  - including 20 with asymptomatic BM
  - 35% of the patients with BM had received previous RT to the brain
Ipilimumab + Fotemustine

- 40 patients in the study population achieved disease control (47%), as did 10/20 patients with BM (50%).
- Of the 13 patients with BM who did not have previous radiotherapy, 5 (38%) of them had a complete response in the brain.
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Combinations: Radiation therapy (RT)

- RT induces damage to the BBB and the tumor DNA → increases tumor immunogenicity

- Clinical experience: Ipilimumab + stereotactic radiosurgery (SRS)

- 77 patients with metastatic melanoma underwent SRS
  - 27 of them had ipilimumab (before or after SRS)

- Median survival
  - 21.3 vs. 4.9 months in those who received ipilimumab vs. those who did not

Knisely 2012 J Neurosurg
## Combinations: Ipilimumab + RT

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<th>No Ipilimumab (n=37)</th>
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<td>16</td>
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<td>SRS</td>
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- A retrospective study of 70 patients with melanoma brain metastases treated with RT
- 33 patients received ipilimumab
  - Either before or after RT
  - Mostly sequential, 5 patients treated concurrently

Silk, et al, 2013, Cancer Medicine
Improved survival with ipilimumab and SRS

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Ipilimumab is associated with significantly decreased risk of death
HR = 0.43, p = 0.005

Silk, et al, 2013, Cancer Medicine
Ipilimumab appears to impact survival in patients treated with SRS

Median survival (in months) from the date of RT

<table>
<thead>
<tr>
<th></th>
<th>N=</th>
<th>Not treated with Ipilimumab</th>
<th>Treated with Ipilimumab</th>
<th>Difference</th>
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<td>Silk <em>et al</em> 2013</td>
<td>70</td>
<td>4.0</td>
<td>19.9</td>
<td>15.9 months</td>
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Future directions

- PD-1 and PD-L1 antibodies

- Checkpoint inhibitors + RT

- Vaccines: DC/cell-based vaccines, oncolytic viruses

- Adoptive T cell strategies:
  a) CAR-T targeting EGFR
  b) Anti-CD3 X anti-EGFR armed T cells (EGFR BATs)

- Combination therapies of checkpoints, adoptive T cells, RT, and/or vaccines
Lessons and Take Home Messages

- Immunotherapy has a therapeutic advantage over cytotoxic drugs in CNS tumors because T-cells can cross the BBB.

- The BBB is not absolute. Memory T cells provide immune surveillance in the CNS and mediate inflammation in response to antigens.

- Combinations of immunotherapies and/or immunotherapy in combination with radiation therapy may be effective for preventing or treating BM in many types of cancer.
THANK YOU!!
Select anti-PD-1 studies in BM

- MK-3475 (Pembrolizumab) in Melanoma and NSCLC Patients With Brain Metastases
  - ClinicalTrials.gov Identifier: NCT02085070

- A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects With Melanoma Metastatic to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab Monotherapy (CheckMate 204)
  - ClinicalTrials.gov Identifier: NCT02320058