Emerging Role of Immunotherapy in Metastatic Merkel Cell Carcinoma (MCC)

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Objective

• General Background
  – Epidemiology, Pathogenesis
  – Merkel Cell Polyomavirus
• Management of MCC
  – Surgery, Radiation
  – Chemotherapy, Immunotherapy
• Recent Immunotherapy Trials in MCC
  – Avelumab
  – Pembrolizumab
• Emerging Serologic Testing to Monitor MCC
• MCC Therapeutic Pipeline
• Challenges in MCC
• Case Studies
Background

- Originally thought to derive from the Merkel cell, a mechanoreceptor cell type first described by Friedrich Sigmund Merkel (1845-1919).

- Dr. Toker first described a ‘trabecular carcinoma’ of the skin in 1972; he later related this disease to the Merkel cell based on electron microscopy studies demonstrating the presence of dense-core granules.

- More recent studies suggest that Merkel cell carcinoma is derived from a pluripotent stem cell in the skin.
Background

• Aggressive skin cancer composed of small, round, blue cells that stain positive for neuroendocrine markers including synaptophysin, chromogranin A, as well as CK20 in a ‘dot-like’ pattern.

• 70% of patients present with Stage I/II disease, 25% present with palpable LNs, and 5% present with distant metastases.

• Associated with immunosuppression, UV radiation, male gender, and older age (median age of diagnosis at 75).

• ~2000 new cases diagnosed annually in the U.S. based on 2015 census data.

• MCC is a chemosensitive disease associated with a high risk of recurrence.

• Historical retrospective studies have demonstrated 5 year overall survival = 0-18%.

http://www.pathologyoutlines.com
Background

• ~80% of cases have also been associated with the Merkel Cell Polyomavirus (97% based on PCR).

• Immunosuppression seems to allow for Merkel Cell Polyomavirus oncogenesis.

• MCPyV integrates into the genome of target cells and drives cellular proliferation via expression of the large T antigen and sequestration of the RB protein.

• MCPyV-negative MCCs develop in response to prolonged radiation exposure; associated with higher mutational burden characteristic of a UV damage signature.

Staging

- **Stage I** – Primary tumors ≤ 2 cm
- **Stage II** – Primary tumors > 2 cm or a primary tumor with invasion into bone, cartilage, muscle, or fascia
- **Stage III** – Any primary tumor with regional lymph node involvement
- **Stage IV** – Metastasis beyond the regional lymph nodes
Management of MCC

• **Stage I and II MCC**
  - Wide local excision with $\geq 1$ cm margin
  - Sentinel Lymph Node Biopsy (SLNBx)
    - $\sim 20\%$ of T1 MCC, $\sim 50\%$ of T2 MCC exhibit nodal metastases\(^1\)
    - Node-positive MCC patients exhibit inferior clinical outcomes
    - Completes pathologic staging, informs prognosis, and guides clinical trial referral
    - Provides therapeutic benefit by surgically removing the involved node; risk of disease recurrence is 3.5x lower in patients who undergo SLN biopsy compared to those who do not
    - **All clinically node negative patients, including those with small primary lesions, should undergo a SLNBx\(^2\)**
      - False-negative rate of SLNBx in MCC is estimated to be $\sim 15$-20% $\rightarrow$ high-risk patients with negative SLNBx should be considered for adjuvant radiotherapy to the lymph node bed\(^3\)

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Management of MCC

• **Stage III MCC**
  – 1/3 of MCC patients present with node-positive disease
  – Complete LN dissection recommended when feasible\(^1\)
  – Patients with clinically positive nodes have a 5 year disease-specific survival of ~50\(^2\)
  – Adjuvant radiation therapy is recommended in the presence of extra-capsular extension or multiple node involvement
  – Concurrent chemoradiation found to be beneficial in the setting of high-risk head & neck disease based on a retrospective review of 4,815 patients\(^3\)
    • Positive margins, male gender, primary tumor size ≥ 3 cm
  – Clinical trial referral

Management of MCC

• **Stage IV MCC**
  – Chemotherapy
    • Carboplatin/etoposide regimen
    • First line setting response rates between 53-61%; however, these responses lack durability (median duration of response of 85 days)
    • Second line setting response rates reported at ~23%
    • Alternative regimens: carboplatin, topotecan, CAV
  – Immunotherapy
JAVALUE Phase II Clinical Trial

- Multicenter, open-label, single group, phase II clinical trial enrolled patients with Stage IV Merkel cell carcinoma refractory to at least one line of chemotherapy.
- Patients with HIV, immunosuppression, or previous solid organ transplants were excluded.
- Patients received avelumab, a human anti-PD-L1 IgG1 monoclonal antibody, at 10 mg/mL by 1 hr infusion once every 2 weeks.
- Radiological assessment performed every 6 weeks per RECIST version 1.1.
- Confirmation of progression was confirmed by a repeat 6 week scan.

JAVELIN Phase II Clinical Trial

- 88 patients were enrolled and treated with avelumab between July 25, 2014, and September 3, 2015
  - 41% had received two or more previous lines of therapy
  - 53% had visceral metastases
- Median follow-up was 10.4 months
- 79% were PD-L1-positive (>1% positive tumor cells)
- 60% were Merkel cell polyomavirus-positive

### Confirmed best overall response* (n=88)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Count (Percentage)</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (10%)</td>
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<tr>
<td>Progressive disease</td>
<td>32 (36%)</td>
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<tr>
<td>Non-complete response/ non-progressive disease†</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Non-assessable‡</td>
<td>18 (20%)</td>
</tr>
<tr>
<td><strong>Objective response</strong> §</td>
<td><strong>31.8% (21.9–43.1)</strong></td>
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- Response duration lasting at least 6-months: 29%
- 6.7% 6-month durable response rate to chemotherapy in refractory MCC patients

JAVELIN Phase II Clinical Trial

JAVELIN Phase II Clinical Trial

• Median PFS = 2.6 months
• Median OS = 11.3 months
• 6 month survival = 69%
• 18 month survival = 30%
• Median time of response = 6 weeks

• PD-L1-positive: 34.5% ORR
• PD-L1-negative: 18.8% ORR
• MCPyV-positive: 26.1% ORR
• MCPyV-negative: 35.5% ORR

### JAVELIN Phase II Clinical Trial

- Treatment-related adverse events occurred in 70% of patients
- Grade 3 AEs in 5%; no deaths on study
- 2/88 patients discontinued therapy

<table>
<thead>
<tr>
<th></th>
<th>Grade 1–2</th>
<th>Grade 3</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>21 (24%)</td>
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<tr>
<td>Infusion-related reaction*</td>
<td>15 (17%)</td>
<td>0</td>
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<tr>
<td>Diarrhoea</td>
<td>8 (9%)</td>
<td>0</td>
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<tr>
<td>Nausea</td>
<td>8 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>5 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increase</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>2 (2%)</td>
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<tr>
<td>Blood cholesterol increase</td>
<td>0</td>
<td>1 (1%)</td>
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<tr>
<td>Aminotransferase increase</td>
<td>0</td>
<td>1 (1%)</td>
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<tr>
<td>Potential immune-mediated treatment-related adverse event†</td>
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<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (3%)</td>
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<tr>
<td>Hyperthyroidism</td>
<td>2 (2%)</td>
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<tr>
<td>Pneumonitis</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1 (1%)</td>
<td>0</td>
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[accc-iclio.org](https://accc-iclio.org)
CITN-09 Phase II Clinical Trial

- Multicenter, open-label, single group, phase II clinical trial enrolled untreated patients with either Stage IV or recurrent locoregional Merkel cell carcinoma that is not amenable to surgery.

- Patients with an immunodeficiency or undergoing treatment with systemic immunosuppressive therapy were excluded.

- Patients received pembrolizumab, a humanized anti-PD-1 IgG4 monoclonal antibody, at 2 mg/kg IV every 3 weeks.

- Radiological assessment performed at 12 weeks and then every 9 weeks per RECIST version 1.1.

CITN-09 Phase II Clinical Trial

- 26 patients with either Stage IIIB (8%) or IV (92%) MCC were enrolled between January 2015 and December 2015
- Median follow-up was 33 weeks
- 65% were Merkel cell polyomavirus-positive

- 56% ORR (4 CR, 10 PR)
- 12/14 responses ongoing
CITN-09 Phase II Clinical Trial

- Median PFS = 9 months
- PFS at 6 months = 67%

- MCPyV-positive: 62% ORR
- MCPyV-negative: 44% ORR
- Treatment-related adverse events occurred in 77%
- Grade 3/4 AEs in 15%
- 2/26 patients discontinued therapy

CITN-09 Phase II Clinical Trial

- No association between pre-treatment PD-L1 expression levels and responses to pembrolizumab
- MCPyV status correlates with PD-L1 expression status


accc-iclio.org
Serologic Testing to Monitor MCC

- Overall recurrence rate of MCC is >40%.
- Serologic testing for MCC is based on the development of antibodies to a Merkel Cell Polyomavirus (MCPyV) large T antigen oncoprotein (6 cc blood sample required).
- ~50% of patients with a new diagnosis of MCC exhibit evidence of this antibody (higher rates in patients with occult primary lesions).
- <1% in patients without MCC.
- Patients with detectable MCPyV antibodies exhibit a 42% lower risk of disease recurrence.

https://www.merkelcell.org/testing-and-diagnosis/serology/

Paulson, K. et al. Cancer Res. 2010. 70:
Serologic Testing to Monitor MCC

- Patients with detectable MCPyV antibodies exhibit a 42% lower risk of disease recurrence.
- Falling titers have a 97% negative predictive value for disease recurrence.

https://www.merkelcell.org/testing-and-diagnosis/serology/
Serologic Testing to Monitor MCC

Patients with No Disease Recurrence
- Ab levels typically decrease by >90% within one year after Tx

Patients with Disease Recurrence


https://www.merkelcell.org/testing-and-diagnosis/serology/
Serologic Testing to Monitor MCC

- Recommended to obtain MCPyV serologies within 2-3 months of initial diagnosis as a baseline measurement

- No detectable MCPyV antibody:
  - 40% higher risk of disease recurrence
  - Suggests that more frequent imaging is necessary to monitor disease

- Detectable MCPyV antibody:
  - Can track disease recurrence using serologic testing
  - Suggests that imaging can be less frequent when monitoring this disease
MCC Therapeutic Pipeline

- Avelumab 10 mg/kg IV every 2 weeks + local radiation vs IT IFN-α + MCPyV TAg-specific CD8+ T cells in patients with Stage IV MCC (phase I/II study, NCT02584829)

- Ipilimumab 1 mg/kg IV every 6 weeks + nivolumab 240 mg IV every 2 weeks ± SBRT in patients with Stage IV MCC (randomized phase II study, NCT03071406)

- TVEC ± local radiation for patients with unresectable Stage III or IV MCC (randomized phase II study, NCT02819843)

- Activated NK cell (NK-92) infusion + IL-15 (ALT-803) in patients with unresectable Stage IIIIB or IV MCC (phase II study, NCT02465957)

- Adjuvant ipilimumab 3 mg/kg therapy x 4 doses vs observation for previously resected MCC (randomized phase II study, NCT02196961)
Current Challenges

• anti-PD-1/PD-L1 antibody-refractory MCC patients
  – Intra-lesional therapeutic strategies to induce MCC antigen-specific CD8+ T cell clones
  – Combination immunotherapy regimens may be difficult in this patient population

• Immunosuppressed patients
  – Alternative treatment strategies may be necessary

• Patients with comorbid autoimmune diseases
  – Anti-PD-1/PD-L1 antibody therapy should be considered
  – Vaccine/tumor antigen-directed therapies reasonable to consider

• Intra-cranial metastases
Case Study #1

80 yo male with a h/o SCC of the head & neck treated with neoadjuvant chemoradiation and surgical excision, presenting with a new right-sided neck nodule

- Tissue biopsy showed a 0.7 cm small, round, blue cell tumor staining positive for synaptophysin, CD56, and CK20 (TTF-1 negative) with positive margins; interpreted to be c/w MCC
- PCR negative for MCPyV
- PET CT showed right-sided parotid nodule with no mild FDG uptake and no evidence of distant disease
- ENT noting a 3 cm right-sided cervical mass on exam; underwent a radical excision of the soft tissue mass and a right-sided parotidectomy
  - Gross evidence of intra-dermal and intra-lymphatic disease noted
- Initiated on carboplatin/etoposide chemotherapy; completed 4 cycles (was not eligible for additional radiation therapy)
Case Study #1

- PET CT imaging showing evidence of local disease recurrence
- Initiated on avelumab 10 mg/kg IV every 2 weeks on the phase II JAVELIN 200 clinical trial
- Noted to have near complete gross response after 3 doses of avelumab
- Completed regimen with no gross or pathologic evidence of disease
- PET CT imaging 2 years later showing continued CR
Case Study #2

75 yo male diagnosed with MCC over his right calf in March 2011. Primary lesion was chromogranin and synaptophysin positive but CK20 and TTF-1 negative. Underwent WLE and SLNbx which was negative. Underwent local radiation therapy at the tumor bed.

- Presented with AMS and disorientation in March 2017; brain MRI showing multiple enhancing supratentorial lesions with surrounding vasogenic edema
- IC lesion biopsy c/w a neuroendocrine carcinoma positive for synaptophysin, enolase, CD56 (CK20, TTF-1 negative)
- Treated with WBRT – 3 Gy x 10 fractions
Case Study #2

- Repeat PET CT showing enlarging right apical pulmonary nodule, now FDG avid, along with a new 1 cm FDG avid lesion in the caudate lobe of the liver
- Initiated on avelumab 10 mg/kg IV every 2 weeks
- After 4 doses, clinically asymptomatic with improved energy and no neurologic complications; brain MRI showing no evidence of disease recurrence and significant improvement in vasogenic edema; PET CT demonstrating complete hepatic response with stable right apical lung nodule

Before Treatment  After 4th Cycle
Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at accc-iclio.org