Immunotherapy for Merkel Cell Cancer

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Outline

Merkel cell cancer: presentation, impact, pathogenesis
Adjuvant therapy: + radiation, - chemotherapy, ADAM clinical trial
Monitoring for recurrence: serology assay
Advanced MCC: Checkpoint inhibitors in 1st line per 2018 NCCN
T cell therapies for MCC
  • Current trials: endogenous T cell therapy
  • Sharing cures: transgenic T cell therapy
Questions
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Merkel cell carcinoma

- Aggressive neuroendocrine skin cancer
- Typically presents as a red or purple, rapidly growing nodule
- Incidence increased 3-10 fold in immunosuppressed populations, & outcomes worse in these populations
- HOWEVER 90% of cases diagnosed in immunocompetent

Images: Paul Nghiem
1. Heath et al JAAD 2008
2. Paulson et al JID 2013
MCC Incidence Increasing: 2500 cases/year in USA

Cases Reported to SEER-18 (% cases in year 2000)

- MCC +95%
- Melanoma +57%
- All Solid Tumors +15%

Year

2000 2005 2010

B.

SEER database
MCC incidence will continue to grow as baby boomers age into MCC risk groups.

**Baby boomers 2015**

**Baby boomers 2025**

**Melanoma (per 6.7K)**

**MCC (per 100K)**

**Age at Diagnosis (Years)**

**US Annual Incidence Rate (Sex Adjusted)**

- Melanoma (per 6.7K)
- MCC (per 100K)

**MCC Incidence in US (# Cases)**

**Year**

Calculated from Observed SEER-18 Incidence Rates
Projected based on US Census Data

Paulson et al, JAAD, in revision
MCC risk factors

Age
Male sex
UV exposure
Immune suppression

**Merkel cell polyomavirus – 80% of cases**

Discovered in 2008 by Patrick Moore and Yuan Chang at U. Pitt (who also discovered KSHV)

Feng et al – Science 2008
MCPyV – a common virus that breaks in a rare and special way to cause MCC

Virus associated MCCs are addicted to oncoprotein expression

The virus in MCC tumors is broken and no longer contagious
MCC Staging: Stage III B “unknown primary”

- Up to 50% of patients presenting with stage III B (palpable nodal, no distant) MCC have no identifiable skin primary

- These patients are thought to have had an immune response leading to regression of a small skin primary

- Consistent with this, outcomes are better in this group

Chen et al, Am J Surg
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Risk of MCC recurrence is high! This is true even for early stage disease.

Nghiem et al, merkelcell.org

Paul Nghiem, MD
Adjuvant radiation typically indicated: improved RFS and OS

*Bhatia S et al, JNCI, 2016*
Adjuvant chemotherapy does not help and may hurt

No clear survival benefit in any of the studies that have looked at adjuvant chemotherapy for MCC, even when stratifying to stage III disease (eg. Bhatia S et al, JNCI 2016)

Based on emerging data, chemotherapy may reduce responsiveness to subsequent immunotherapy should recurrence develop....
Adjuvant immunotherapy is being tested

ADAM trial:
- Stage IIIB (palpable nodal) disease, within 4 months of surgical excision
- +/- radiation therapy OK
- 100 patients, randomized 1:1 placebo vs. avelumab (PD-L1 blockade)
  - 2 years treatment -> 3 years follow-up
- 14 US sites, being led by SCCA
- Opens soon – we appreciate your kind referral of potentially eligible stage IIIB patients as we try to accrue for this rare disease!
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Biomarkers for recurrence

Immunotherapy works better at lower burdens: rationale for early detection of recurrent disease

Good biomarkers amplify underlying cancer signal to help differentiate signal to noise

The immune system is a great amplifier

Virus positive MCCs have a shared antigen (viral oncoprotein)
Serologic assay for MCC (“AMERK”)

At presentation, ~50% of patients have circulating antibodies to Merkel cell polyomavirus oncoproteins (T Antigens)
- <1% of healthy individuals have these antibodies

Seronegative patients have a high recurrence risk
- Mixed group of virus negative patients and poor immune response to MCC patients

For seropositive patients, serial antibody titers can be used to detect recurrence

Paulson, Carter et al, Cancer Res 2010
Paulson et al, Cancer, 2017
Sample patients

**NED**

- **Patient #1**
- **Patient #2**
- **Patient #3**

**Recurrence**

- **Patient #4**
- **Patient #5**
AMERK is clinically available (UW labmed) & listed as an option in 2018 NCCN guideline

If testing:
• Check initial level within 90 days of diagnosis – levels fall fast
• Only check serial levels if initially seropositive
• Validated only for detection of first recurrence, not for monitoring response to immunotherapy or detecting subsequent recurrences

Ordering: http://www.merkelcell.org/sero

Conflict of interest statement: I was involved in the development of this assay. I have no personal financial interest in this.
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Durability of chemotherapy response historically poor: additional treatment options needed

$n = 62$ (All cases)
Median PFS: 94 days

"Time from start of 1st line chemotherapy (days)"
"PFS (%)"
All MCC is immunogenic

80% (MCPyV+): Addicted to immunogenic viral oncoproteins
20% (MCPyV-): Higher mutational burden than any cancer type in TCGA (Goh et al, 2016)
Checkpoint inhibitors are effective in advanced MCC

Pembrolizumab (1<sup>st</sup> line)
- PD-1 inhibitor, q3 weeks, under FDA review for this indication
- RR 56%

Avelumab (2<sup>nd</sup> line)
- PD-L1 inhibitor, FDA-indicated, q2 weeks
- RR 32%

Ngheim et al NEJM 2016
Kaufman et al Lancet Oncol 2016
Toxicities of checkpoint inhibitors are similar in MCC as to other cancers: fatigue, iRAEs including are severe autoimmune reactions
Checkpoint inhibitors are now first line in 2018 NCCN guideline

NCCN Guidelines Version 1.2018
Merkel Cell Carcinoma

PRINCIPLES OF SYSTEMIC THERAPY

Local Disease:
• Adjuvant chemotherapy not recommended

Regional Disease:
• Clinical trial (preferred)
• Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
  ▶ Cisplatin ± etoposide
  ▶ Carboplatin ± etoposide

Disseminated Disease:
• Clinical trial (preferred)
• Avelumab<sup>2</sup>
• Pembrolizumab<sup>2</sup>
• Nivolumab<sup>2</sup>
• As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  ▶ Cisplatin ± etoposide
  ▶ Carboplatin ± etoposide
  ▶ Topotecan
  ▶ (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine
Great progress, but we can do even better…

Types of clinical responses to checkpoint blockade….

- **Primary refractory** (never responded)
- **Acquired resistance** (lost response)
- **Long-term response** (immunologic cure)
Poor T cell infiltrate (n=120)

Strong T cell infiltrate (n=26)

no T cells

MCC outcome, whereas peritumoral lymphocytes are not. This is also true for other cancers, such as ovarian cancer and colon cancer.

Second, immunohistochemical CD8+/H11001 evaluation may be more sensitive and specific for identification of TILs than routine histology. This is because T cells can sometimes be indistinguishable from MCC tumor cells using hematoxylin and eosin staining.

This study has several limitations despite the fact that it is both the largest molecular and immunohistochemical examination of MCC yet reported, to our knowledge. The median age of the patient population (66 years) was younger than that for MCC nationally (76 years).

Fig 3. T-cell infiltration and Merkel cell carcinoma (MCC)–specific survival in an independent set of 146 patients. (A) Tumor infiltrating lymphocytes (TILs) analysis by routine histology among 129 patients. (*) TILs were prognostically significant on univariate (P/H11005 .03) but not multivariate (P/H11005 .12) analysis. (B) Intratumoral (IT) CD8+/H11001 lymphocyte infiltration. Brisk CD8s were defined as an intratumoral CD8 score of 3 to 5 (corresponding to approximately 60 or more CD8s per typical 40X high power field), sparse as 0 to 2. (†) IT CD8 infiltration was a statistically significant predictor of outcome on univariate (P/H11021 .01) and multivariate (P/H11005 .01) regression analyses (Table 3). (C) Subgroup breakdown of (B), by extent of disease at presentation (as indicated).Extent of disease at presentation was not known for two patients. Statistical analysis was not performed on subgroups; instead, multivariate Cox regression is listed in Table 3.

Table 3. Multivariate Cox Regression Analysis Demonstrates Intratumoral CD8 Score Is an Independent Predictor of Merkel Cell Carcinoma Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate HR 95% CI</th>
<th>P</th>
<th>Multivariate HR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II v I</td>
<td>0.8 0.1 to 5.0</td>
<td>.86</td>
<td>1.1 0.2 to 6.6</td>
<td>.92</td>
</tr>
<tr>
<td>III v I</td>
<td>6.5 1.9 to 22.6</td>
<td>.01</td>
<td>5.5 1.4 to 21.2</td>
<td>.02</td>
</tr>
<tr>
<td>IV v I</td>
<td>18.8 3.4 to 104.5</td>
<td>.01</td>
<td>31.5 6.8 to 147.0</td>
<td>.01</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.4 0.1 to 1.0</td>
<td>.06</td>
<td>0.6 0.2 to 1.7</td>
<td>.31</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.1 0.5 to 2.3</td>
<td>.87</td>
<td>0.8 0.4 to 1.8</td>
<td>.62</td>
</tr>
<tr>
<td>CD8, per increase on 0 to 5 scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritumoral</td>
<td>0.8 0.6 to 1.0</td>
<td>.06</td>
<td>0.9 0.6 to 1.4</td>
<td>.79</td>
</tr>
<tr>
<td>Intratumoral</td>
<td>0.5 0.5 to 0.7</td>
<td>.01</td>
<td>0.5 0.3 to 0.9</td>
<td>.01</td>
</tr>
</tbody>
</table>

NOTE. CD8+/H11001 scoring scale is described in Methods and in the scoring guide provided as a Data Supplement. All variables listed in this table were included in the multivariate analysis.

Abbreviation: HR, hazard ratio.
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Endogenous Cellular Therapy Targeting MCPyV

- Patient Leukapheresis
- Enrich with peptide-pulsed dendritic cells
- Peptide = small piece of target antigen (MCPyV)
- ‘Outgrowth’ of antigen-specific T cells
- GMP flow sorting
- Expansion
- Infuse virus-specific, highly expanded T cells back into patient ($10^{10}$ per m$^2$)

Production time: ~4-6 weeks

Dr. Aude Chapuis
How CD8+ T cells ("cytotoxic T lymphocytes") work:

Signal 1 = Trigger

Signal 2 = Safety

Target cell

Peptide antigen

CD8

TCR

Class I MHC molecule (HLA)

i.e. T-cell receptor

Perforin

Granzymes

Cytotoxic T cell (CTL)

Target cell

Pore

Released cytotoxic T cell

Dying target cell

Target cell

PD1

OFF – NO KILLING

Target cell

PD1

ON – KILLING
Combination immunotherapy for advanced MCC

Signal 1 = Trigger

Signal 2 = Safety

Our current T cell therapy trials have three parts (triple therapy):

1) CD8+ T cells (virus specific)
2) Class I MHC upregulation
3) Checkpoint inhibition
Infused T cells Persist and Function

- **Grey lines**: with PD1 axis blockade
- **Black lines**: without PD1 axis blockade

**Graph A**: Time from first T-cell Infusion (days)
- PD
- CR

**Graph B**:
- **% Expression**
- **Phenotype**
- **Cytokine secretion**
- T CM
- T EM
- T TD
- PD-1
- IFN
- TNF
Infused MCPyV T cells preferentially localize to tumor

Tumor burden:  

### Tumor burden:  

<table>
<thead>
<tr>
<th>Pre-Treatment</th>
<th>&lt;1 month</th>
<th>~6 months post Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>% detected infused clonotypes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td># detected infused clonotypes</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

- **Peripheral Blood**
- **MCC Tumor**

*Remainder:* Infusion product
Infused T cells trigger epitope spreading

- LT-Ag protein
- sT-Ag protein
- Common T
- LT-Ag Unique
- sT-Ag Unique

4) CD8+ and CD4+ T cells are assessed for IFN-Y production by ICS

Patient 9245-1 (CR)
CD4+ Epitope Spreading

Patient 9245-3 (CR)
CD8+ Epitope Spreading

Reactive Sample

100-fold expansion of non-infused MCPyV Reactive Cells
Encouraging responses to endogenous cell therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>HLA-upreg</th>
<th>Targeted MCPyV epitope</th>
<th>Grade 3/4 AEs</th>
<th>Best Response (RECIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9245-1</td>
<td>XRT</td>
<td>HLA-A24 “EWW”/B07 “APN”</td>
<td>Lymphopenia</td>
<td>CR (ongoing @ 14mo)</td>
</tr>
<tr>
<td>9245-2</td>
<td>IFN</td>
<td>HLA-A02 “KLL”</td>
<td>Lymphopenia</td>
<td>CR (ongoing @ 15mo)</td>
</tr>
<tr>
<td>9245-3</td>
<td>IFN + XRT</td>
<td>HLA-A02 “KLL”/B35 “FPW”</td>
<td>Lymphopenia, CRS</td>
<td>CR (ongoing @ 12mo)</td>
</tr>
<tr>
<td>9245-5</td>
<td>XRT</td>
<td>HLA-A02 “KLL”</td>
<td>Lymphopenia</td>
<td>PR (progressed @ 3 mo)</td>
</tr>
<tr>
<td>9245-6</td>
<td>IFN</td>
<td>HLA-A02 “KLL”</td>
<td>Lymphopenia</td>
<td>PD</td>
</tr>
</tbody>
</table>

Complete regressions in 3 patients that had persistence of the infused T cells – all ongoing at > 1 year

In patients who the T cells did not persist, outcomes were worse

Paulson et al., ASCO 2017
Responses by iRRC

Response in Tumor Burden (irRC)

Change in Tumor Burden (%)

Time from Treatment Initiation (Months)

Stable Disease

Closed Symbols = Received T cells

- 9245-1
- 9245-2
- 9245-3
- 9245-4
- 9245-5
- 9245-6
T cells plus avelumab plus single fraction radiation to one lesion confirmed CR at all cancer sites

- Patient with ongoing CR 21 months after Triple Therapy
- Tolerated all study infusions without toxicity
Limitations of endogenous cell therapy

- Slow
- Expensive
- Difficult to deliver intended doses...
- Dependent on the patient’s underlying immune response
  - Patient may have poor avidity or absence of underlying T cell responses
Transgenic T cell Therapy

Patient

Leukapheresis

T cells (autologous/self)

TCR transduce (lentivirus)

GMP flow sorting

Non-specific expansion

Total production time: ~3 weeks

Dr. Aude Chapuis
What TCR do you want? Sharing Cures

Tumor burden:

+++  ++  0

Patient 9245-3
Pathologic CR 18 months after therapy start

% detected infused clonotypes

# detected infused clonotypes

Peripheral Blood
MCC Tumor

Pre-Treatment
<1 month Post-Treatment
~6 months post Treatment (in CR)
Problem: TCR alpha and beta on different chromosomes

Solution: Single Cell RNA sequencing
ATTACk-MCC Regimen: In development, anticipating enrollment in 2018

- 16 patients over 2 years
- Autologous
- Transgenic T cells
- Velumab
- Class I MHC upregulation
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FHCRC

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Andy Marty, PhD

Dr. David Koelle

Clinical Team

Kieu-Thu Bui

Judy Delismon

Cari Morin

Susan Lemmon

Ana Radu

Melanoma/Renal RNs

Skin Oncology RNs

Thank you!!!!