Summary of 10th Annual MMIG Meeting

(Merkel cell carcinoma Multi-center Interest Group)

Friday March 20th, 2015
American Academy of Dermatology Annual Meeting
San Francisco, CA
Prepared by Drs. Erica Shantha & Paul Nghiem

Announcements:

1) If anyone is interested in presenting at next year's MMIG meeting in Washington, DC on March 4th, 2016 (Friday 5 – 7 pm), please send Paul an email (pnghiem@uw.edu) with a proposed topic that is relevant to MCC patient care or translational research.

Speakers/Topics (detailed in following pages):

1. **Update on clinical trials in MCC — Active & Planned**
   Erica Shantha, UW/Seattle

2. **Blood-based screening for MCC using circulating tumor cells, chromogranin A, and neuron-specific enolase: what's useful, what's not?**
   Isaac Brownell**,** NCI/ Bethesda

3. **Does polyomavirus presence or absence in the tumor affect survival in MCC?**
   Paul Nghiem, UW/Seattle

4. **Updates on AJCC staging of MCC**
   Arthur Sober**,** MGH/Harvard/Boston & Chris Bichakjian, UM/Ann Arbor

5. **How does surgical margin size affect local recurrence in MCC?**
   Teresa Fu, Stanford/Palo Alto

1. Update on clinical trials in MCC — Active & Planned

Erica Shantha, UW/Seattle

Actively Recruiting:

Anti-PD-1 in "first line:"

- The Phase II trial of anti-PD-1 (pembrolizumab) (http://clinicaltrials.gov/ct2/show/NCT02267603?term=citn-09&rank=1) for first line therapy of advanced MCC is currently recruiting and target enrollment is 24 patients (10 patients enrolled). This trial is currently open in Seattle, Mount Sinai, Johns Hopkins, Stanford, and Emory, with more sites to come.

Anti-PD-L1 in "second line:"

- The EMD Serono Phase II trial of anti-PD-L1 (Avelumab) (https://clinicaltrials.gov/ct2/show/NCT02155647?term=pd-l1&rank=18) as second line therapy for advanced MCC is recruiting with target enrollment of 84 patients. 53 patients have been enrolled and 39 patients continue to receive treatment. The trial is open at 47 sites including 16 sites in the United States including Seattle, Rutgers, Tennessee Oncology, the Angeles clinic in LA, UCLA, NCI, Memorial Sloan Kettering, MD Anderson, Mount Sinai, Moffitt, Fox Chase Ca Ctr, Stephenson Oklahoma Ca Ctr, Dana Farber, and U of Pittsburgh.

Ipiliumumab Adjuvant therapy Trial:

- In Europe, the Bristol-Myers Squibb Phase II trial of adjuvant therapy of completely resected MCC with Ipilimumab is now recruiting patients. Patients are randomized to placebo vs. ipilimumab (https://clinicaltrials.gov/ct2/show/NCT02196961?term=ipilimumab&rank=28).

Adoptive T cell Therapy:

- The MCPyV-reactive autologous T cell therapy for metastatic MCC phase I/II trial at the Fred Hutchinson Cancer Research Center is currently being revised to combine this therapy with anti-PD-L1 with the hope of improving efficacy. This trial may begin enrolling by fall 2015 with combined T cells and anti-PD-L1 (https://clinicaltrials.gov/show/NCT01758458).

Fully Enrolled:

Intralesional IL-12:

- A Phase II trial of intratumoral injection of Interleukin-12 Plasmid and in Vivo Electroporation (https://clinicaltrials.gov/ct2/show/NCT01440816?term=IL-12+electroporation&rank=1) has finished enrollment with 15 patients. Responses at treated lesions were frequent and some responses were noted in untreated tumors. Data analysis is ongoing.

Intralesional TLR4 agonist:

- The Phase I single arm, proof of concept trial with intralesional GLA, a Toll like Receptor 4 agonist (https://clinicaltrials.gov/ct2/show/NCT02035657?term=GLA&rank=25), has completed enrollment with 10 patients. Although preliminary, there have been some encouraging responses.

The presentation ended with two exciting and encouraging patient responses (one PD-1 patient, one PD-L1 patient) from Seattle. The first patient was a 70 yo F diagnosed with stage IV disease involving two subcutaneous lesions on her right lower extremity and multiple abdominal/pelvic masses compressing her bladder. She was experiencing abdominal discomfort and urinary frequency secondary to tumor compression on her bladder. After one dose of anti-PD-1 her subcutaneous lesions disappeared (pathologically confirmed at 3 weeks) and her clinical symptoms resolved in 2 weeks. At 12 weeks, radiologic confirmation revealed a 54% reduction in target tumors by RECIST measurement and she continues on trial.

The second patient is a 55 yo F who presented with Stage IV disease involving the liver. She initially

completed 4 cycles of chemotherapy which resulted in a mixed response. Two months after chemotherapy, multiple tumors in the liver had progressed (measuring up to 11 cm in size). Four weeks into PD-L1 therapy, her liver tumors decreased to half their size. Therapy is ongoing and the treatment has been well tolerated.

References:

Afanasiev *et al,* Clin Ca Research 2013 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790865/)
Chapuis *et al*, Ca Immunology Research 2014
(http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pmc/articles/PMC3888869/)

2. Blood-based screening for MCC disease burden using circulating tumor cells, chromogranin A (ChrA), and neuron-specific enolase (NSE): what's useful, what's not?

Isaac Brownell, NCI/ Bethesda

Dr. Brownell outlined the need for useful biomarkers in MCC. ChrA and NSE have been used for the diagnosis, staging, and surveillance of patients with neuroendocrine tumors. Epithelial cell adhesion molecule (EpCAM) positive circulating tumor cells (CTCs) have been used as a prognostic and treatment biomarker for many epithelial tumors, including breast and colon cancer. Dr. Maria Gaiser works in Heidelberg, Germany where they routinely assess NSE and ChrA blood levels when following MCC patients. She had retrospectively identified 60 MCC patients, from 1998 – 2014, that had ChrA and NSE levels, and 30 MCC patients were assayed for CTCs. Dr. Brownell worked with her to examine if these markers were clinically useful.

There were 342 NSE and 367 ChrA blood levels among 60 MCC patients. Neither first NSE levels, average NSE, or max NSE predicted progression free survival (PFS) or disease specific survival (DSS). Similarly, first and max ChrA level did not predict survival. Moreover, these blood levels did not correlate with presence of disease (in patients with NED vs. MCC present), suggesting these markers are not clinically useful.

In MCC, CTCs are characteristically positive for EpCam, CD56, and CK20. Dr. Brownell's team analyzed results from 30 MCC patients and 10 control subjects. EpCAM positive CTC counts correlated with MCC disease status, but were not predictive of stage. However, in 4 patients, CTC counts did trend with MCC disease course; after appropriate treatment of MCC, CTCs decreased, and with recurrence of MCC the CTCs increased.

In summary, NSE and ChrA blood test were not clinically useful indicators of MCC disease status or survival. EpCAM positive CTCs maybe a promising biomarker in the future. A manuscript reporting these results is in revision for publication.

3. Does polyomavirus presence/absence in the tumor affect survival in MCC?

Paul Nghiem, UW/Seattle

Dr. Nghiem discussed controversies surrounding Merkel cell polyomavirus (MCPyV) tumor viral status in MCC with regards to detection, prevalence, and clinical significance. His team has compared 3 methods for detecting MCPyV and determined whether tumor viral status is predictive of outcome. Specifically, several studies have evaluated tumor viral status as determined by either PCR or IHC (using 2 antibodies: Ab3 and CM2B4) and evaluated clinical significance. Several studies have shown no survival difference associated with viral status, while Sihto et al found that virus-positive patients had an improved 5 year overall survival (OS)

compared to virus-negative MCC. Current literature suggests 43% -100% of MCC tumors are virus positive (Garneski et al and Rodig et al).

Dr. Nghiem's team analyzed 282 unique patient tumors with each of 3 optimized methods: DNA-PCR and IHC with CM2B4 and Ab3. Viral status was determined by 'best 2 of 3' outcomes of the three tests. IHC staining was scored using the Allred system scale (from 0-8), and less than 3 was considered virus negative. Less than 1 copy of viral DNA per 100 cells was considered virus negative.

282 unique tumors were analyzed and all 3 tests agreed (either positive or negative) on 59% of samples. The viral status of the remaining 41% of tumors was determined by the 'best 2 of 3' status. Overall, 81% of the MCC tumors were found to be MCPyV positive and 19% were virus negative. Comparing each test individually to the 'best of 2 of 3' determination, CM2B4 was the most specific and Ab3 was the most sensitive (but least specific), as shown in the table below.

MCPyV detection method	Specificity	Sensitivity
CM2B4	0.94	0.88
qPCR	0.81	0.83
Ab3	0.45	0.93

Patients with MCPyV negative tumors had a significantly decreased progression free survival compared with virus positive tumors (p=0.0033) and patients with MCPyV negative tumors had a poorer disease-specific survival (p=0.015).

In summary, 53 of the 282 patient tumors (19%) were virus negative. There was no perfect test to determine viral status, but based on sensitivity and specificity data, CM2B4 performed best in this cohort. Patients with no detectable MCPyV in their tumors had significantly decreased PFS and DSS. Thus, virus negative MCC may represent a more aggressive subtype and may warrant closer clinical follow up.

References:

Busam et al, Am J Surg Path 2009(http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pmc/articles/PMC2932664/)
Rodig *et al*, Journal of Clinical Investigation 2012 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533549/)
Garneski *et al*, J Invest Dermatol 2009 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605200/)
Sihto *et al*, Clin Cancer Res 2011(http://www.ncbi.nlm.nih.gov/pubmed/21642382)

4. Updates on AJCC staging of MCC

Chris Bichakjian & Arthur Sober UM/Ann Arbor & MGH/Harvard/Boston

Dr. Sober reviewed the current 7th Edition staging system and proposed ways in which to improve the 8th edition. He reviewed the timeline for the AJCC 8th Edition, with the upcoming Authoring Wave between 9/14 to 3/15 and Post-Authoring Wave (data collection, statistics, and publishing) taking place from 12/15 to 9/16.

Dr. Bichakjian also discussed the MCC staging system that was created in 2009. He presented validation data from a Seattle based repository (which included 428 patients, 213 with local disease and 215 with nodal or metastatic disease) and the Michigan (UM) MCC cohort (which included 458 MCC patients). The current staging system, specifically sub-staging of regional disease (Stage III), was validated by both the Seattle and UM cohorts. Dr. Bichakjian discussed some possible considerations for the 8th edition, which included number of nodes and sub-staging of IIIB disease with or without a known primary. In the Seattle cohort, which included 111 stage IIIB patients and the UM cohort, which included 22 stage IIIB patients, MCC specific survival was

significantly poorer in Stage IIIB patients with a known primary. Further, multiple studies have shown approximately a 50% survival difference among stage IIIB patients with a known primary versus an unknown primary. Interestingly, within the Seattle based cohort, no patient with an unknown primary MCC had immune suppression, suggesting that elimination of a primary lesion may require intact immune function. Dr. Bichakjian also discussed immunosuppression, LVI, tumor thickness, and ulceration for alternative staging.

In summary, the 8th edition will be drafted over the next year and gives us the opportunity to improve and validate the current system. The most likely area for revision is sub-staging of clinically node positive disease into known or unknown primary lesion status.

5. How does surgical margin size affect local recurrence in MCC?

Teresa Fu, Stanford/ Palo Alto

Dr. Fu recently spent a month in Seattle this past November and found that optimal surgical resection margins in MCC was a common question among patients. Dr. Fu and the Seattle MCC team sought to determine whether surgical margin size impacted local recurrence in MCC patients who did and did not receive radiation to the primary tumor. Current NCCN guidelines recommend excising primary MCCs with margins of "1-2 cm". Prior studies had suggested 2-3 cm margins based on data that suggested larger margins decrease recurrence. Using the Seattle based repository, Dr. Fu investigated the effect of surgical margin size on local recurrence in 154 patients with stage I, II, or IIIA MCC. Patients were categorized by surgical margin size (≤1.0 cm or >1.0 cm) and whether they received radiation therapy (RT) to the primary site. **Among the 42 patients who were not treated with RT to the primary site, zero of the twelve recurred if the surgical margin was >1.0 cm, while nine of thirty recurred with surgical margins ≤1.0 cm (p=0.04). Among patients who received RT to the primary tumor site, surgical margins did not significantly affect local recurrence:** 4% (2/48) of patients with ≤1.0 cm margin and 12% (7/58) of patients with a >1.0 cm margin recurred locally (p=0.08).

In summary, in patients who received adjuvant radiation to the primary tumor, there was no association between surgical margin size and local recurrence. However, in patients who did not receive radiation to the primary tumor, surgical margin >1 cm was associated with reduced local recurrence. There was no significant association between margin size and MCC–specific survival in those who did and did not receive radiation. Therefore, in patients who are anticipating therapy with adjuvant radiation, surgical margins can be quite modest in order to reduce morbidity and avoid excess delay in initiating RT.

References:

Allen *et al,* Annals of Surgery 1999 (http://www.ncbi.nlm.nih.gov/pubmed/?term=Yiengpruksawan+et+al+Arch+Surg+1991+%2B+merkell+cell+carcinoma)
Allen *et al,* J Clin Oncol 2005 (http://www.ncbi.nlm.nih.gov/pubmed/15800320)

In attendance at the San Francisco MMIG meeting:

Bichakjian, Chris
Brewer, Jerry
Brownell, Isaac
Compton, Nic
Fu, Teresa
Gao, Ling
Jaimes, Natalia
Lemos, Bianca
Luo, Su
Nghiem, Paul
Otley, Clark
Paoli, John
Perlis, Cliff
Sober, Arthur
Shantha, Erica
Shinohara, Michi
Swetter, Susan
Thakuria, Manisha
Weiss, Johnathan
Wong, Michael
Yu, Siegrid
Zeitouni, Nathalie

Goals of the Merkel cell carcinoma Multi-center Interest Group (MMIG)

- Promote communication and collaborative studies on MCC
- Enhance access to patient data and specimens
- Expand evidence-based care for MCC

The homepage for MMIG contains photos, meeting summaries and more at:
http://merkelcell.org/MMIG.html

MMIG is funded in part by donations from Merkel cell carcinoma patients.

Please note that in many cases, these summaries reflect unpublished data and are provided to help MMIG members manage their patients and give an overview of what is being done at different centers for care and research.