Summary of 8th Annual MMIG Meeting (2013)

(Merkel cell carcinoma Multi-center Interest Group)

Friday March 1st, 2013
American Academy of Dermatology Annual Meeting
Miami, FL
Prepared by Drs. Paul Nghiem & Jozef Lazar

Announcements:

1) If anyone is interested in presenting at next year's MMIG meeting in Denver please send Paul an email (pnghiem@uw.edu) with proposed topic that is relevant to MCC patient care or translational research.

Speakers/Topics (detailed in following pages):

1) Is it OK to avoid radiation entirely in selected MCC cases?
Paul Nghiem (UW-Seattle) & Chris Bichakjian (Michigan)
(large discrepancies between cohorts make conclusions on this topic difficult!)

2) PET vs CT for Merkel: the Mayo Experience & recommendations
Jerry Brewer / Clark Otley (Mayo)

3) PET vs CT for Merkel: the Harvard Experience & recommendations
Linda Wang (Mercy Medical-Baltimore)

(both groups suggest PET-CT is superior to other imaging modalities for MCC)

4) Towards immune-stimulating clinical trials for MCC
Isaac Brownell (NCI)
(There is progress toward establishing trials of CTLA4, CD137/4-1BB, PD1 & PDL1 in MCC)

5) A clinical trial of adjuvant interferon in Stage III MCC
Mike Wong (USC)

6) Single-dose radiation: palliation of isolated metastases & local immune activation
Paul Nghiem (UW-Seattle)
(Due to time, this was not formally presented, but Dr Nghiem outlined high efficacy and low side effects for this single-dose radiation approach in patients with isolated MCC metastases)

1) Is it OK to avoid radiation entirely in selected MCC cases?

Paul Nghiem (UW-Seattle) & Chris Bichakjian (Michigan)

In their 2006 study, Lewis et al. evaluated 1254 cases of MCC from the literature and observed that adjuvant radiation therapy was associated with lower rates of local (3.7 times less likely) and regional recurrence (2.9 times less likely) compared to surgical resection alone. For certain "low risk" patients, however, some have advocated avoiding adjuvant radiation which is itself associated with morbidity.

Dr. Nghiem outlined his criteria for this "low risk" group to include those with primary tumor ≤ 1cm in diameter, negative pathologic margins, absence of lymphovascular invasion in the primary tumor, absence of profound immune suppression and negative SLNB. In 15 patients meeting all of these criteria, the local regional recurrence rate was 27% (4 patients) with a median time to recurrence of 177 days. In their broader study population of 72 patients (with median size of primary tumor 1cm, 36% negative lymphovascular invasion, 14% positive lymphovascular invasion, 8% immunosuppressed and 4% with positive margins), the overall loco-regional recurrence rate was 39% with a median time to recurrence of 236 days.

Dr. Bichakjian reviewed the Michigan experience of 118 patients with MCC (119 lesions) with a mean follow-up of 28 months who were treated without XRT. The majority of the lesions were less than 1cm in diameter (66 less than 1cm, 41 between 1-2 cm and 12 greater than 2 cm) and SLNB negative (70 negative, 31 positive, 8 attempted). Among these lesions, there were a total of 5 local/satellite "in field" recurrences (4.2%), 2 were between 1-2cm and 3 were >2cm. The total recurrence rate was 22.6% (27/119 lesions). These findings led Dr. Bichakjian to conclude that in their low risk group, adjuvant XRT to the primary tumor site was not indicated to prevent local/satellite recurrence and may not be useful in preventing in-transit/regional or distant recurrences.

The group discussed the major discrepancies between these datasets. Specifically, the Michigan and New York (MSKCC) groups see local recurrence rates of <5% among selected patients treated only with surgery. The broad literature & the Seattle cohorts have rates of local recurrence 5-10 TIMES higher, despite using more stringent criteria in some cases to identify 'low risk' cases to be treated only with surgery. No clear conclusions could be made given the wide discrepancies in the data, but clearly we need more/better data to help resolve when adjuvant radiation therapy should be used.

References: (data from Michigan & Seattle cohorts are not yet submitted).

Lewis, K. G., M. A. Weinstock, et al. (2006). "Adjuvant local irradiation for Merkel cell carcinoma." Arch Dermatol **142**(6): 693-700.

2) PET vs CT for Merkel: the Mayo Experience & recommendations

Jerry Brewer / Clark Otley (Mayo)

In recent years a number of imaging modalities including CT, MRI and PET/CT scanning have been used for staging purposes and to guide treatment recommendations in patients with MCC. Dr. Brewer reviewed his recent retrospective study assessing the utility of these tests in evaluating for regional lymph node involvement in patients with MCC. PET/CT imaging (33 patients) demonstrated a sensitivity of 83% (PPV 91%) and specificity of 95% (NPV 91%), compared to CT alone (69 patients) which yielded sensitivity of 47% (PPV 94%) and specificity of 97% (NPV 68%). Moreover, among the 17 false negatives in the CT group, 5 of these had multiple nodes while PET/CT had only 2 false negatives. Additionally, the CT group upstaged 4 patients but falsely down-staged 4 patients, while PET/CT upstaged 6 patients while falsely down staging no patients and incidentally identifying 3 other previously undiagnosed cancers (prostate, breast, lymphoma). Thus, Dr. Brewer concluded that PET/CT is the preferred imaging modality, using regional lymph node pathologic evaluatino as a reference 'gold standard'. All agreed that SLNB is indicated and that of course no imaging modality can be as sensitive as SLNB.

Reference:

Colgan, M. B., T. I. Tarantola, et al. (2012). "The predictive value of imaging studies in evaluating regional lymph node involvement in Merkel cell carcinoma." J Am Acad Dermatol **67**(6): 1250-1256.

3) PET vs CT for Merkel: the Harvard Experience & recommendations

Linda Wang (Mercy Medical-Baltimore)

Dr. Wang reviewed the 7-year Harvard experience with 270 FDG-PET/CT scans performed in 97 patients with MCC. The patient population had a mean age of 70 years, with all 4 stages represented (relatively large number of stage III patients, 53%). 61 PET/CT scans were performed for baseline staging, while the remaining 209 scans were performed for subsequent management. Importantly, they detected a higher incidence of bone/bone-marrow metastases (33% of patients with distant metastases) as compared to previously published reports (11% of patients with locoregional recurrences and distant metastases). Additionally, 12 patients had bone/bone marrow activity not seen by CT and only identified on PET. Initial PET/CT's were also noted to most often upstage those patients with more advanced disease (i.e. LN involvement). Dr. Wang concluded by advocating for PET/CT imaging in MCC patients given its good sensitivity, and because it is the only single-imaging modality that offers whole-body evaluation of all of the most common sites of MCC metastases including the bone/bone marrow.

References:

Hawryluk, E. B., K. N. O'Regan, et al. (2012). "Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: A study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center." J Am Acad Dermatol. Epub ahead of print.

Voog, E., P. Biron, et al. (1999). "Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma." Cancer **85**(12): 2589-2595.

4) Towards immune-stimulating clinical trials for MCC

Isaac Brownell (NCI)

Dr. Brownell outlined his planned clinical trial evaluating the utility of ipilimumab immunotherapy in patients with MCC. There is literature to support the idea that Merkel cell polyomavirus could function as an immune target in MCC patients since 40% of patients generate antibodies for small T antigen and these correlate with tumor load and because high antibody titers for VPI correlate with progression free survival. The proposed study will be an early phase II, single arm, open-label trial, enrolling patients at the NIH and MSKCC with a goal to enroll patients immediately after cytotoxic chemotherapy. Ipilimumab will be dosed at 10mg/kg IV q3 weeks x 4 cycles, followed by maintenance therapy q12 weeks x 4 for responders. Their goal is to begin enrollment within the next 6 months. Ongoing immunotherapy trials using electroporated *IL-12* and autologous T cell therapy were highlighted. Additional immunotherapy trials for MCC evaluating the role of anti CD-137(4-1BB) and anti PD-1 therapy are also exciting new approaches on the horizon.

References:

Touze, A., E. Le Bidre, et al. (2011). "High levels of antibodies against merkel cell polyomavirus identify a subset of patients with merkel cell carcinoma with better clinical outcome." J Clin Oncol **29**(12): 1612-1619.

Paulson, K. G., J. J. Carter, et al. (2010). "Antibodies to merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients." Cancer Res **70**(21): 8388-8397.

5) A clinical trial of adjuvant interferon in Stage III MCC

Mike Wong (USC)

Dr. Wong proposed that adjuvant interferon α-2B may be beneficial in patients with advanced MCC. He is interested in setting up a single arm phase II study evaluating the utility of interferon in lymph node positive or T4 (tumor invades bone/muscle/fascia/cartilage) patients, status-post resection without adjuvant systemic therapy who have no evidence of immunosuppression or autoimmune disease. This group would receive pegylated interferon α-2B at 6μg/kg q1 week x 8 weeks during the induction phase followed by a maintenance phase for 2 years at 3μg/kg q1 week with plan to dose adjust during maintenance to achieve ECOG PS of 0 or 1. In order to achieve 20% improvement in survival over historical 75% at 1 year, allowing for one-sided type 1 error of 5% and 80% power, he projected that he would need to enroll around 50 patients necessitating a multi-institutional approach.

Reference:

Eggermont, A. M., S. Suciu, et al. (2008). "Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial." Lancet **372**(9633): 117-126.

In attendance at the Miami 2013 MMIG meeting:

Ahronowitz, Iris
Baum, Christian
Bichakjian, Chris
Brewer, Jerry
Brownell, Isaac
Carpio, Vanessa
Choi, Jaehyuk
Gao, Ling
Huang, Victor
Lai, Jennifer
Lazar, Jozef
Liegeois, Nanette
Lucero, Hanna
Martinez, John Carlos
Nghiem, Paul
Olerud, John
Raghu, Preethi
Roa, Francisca
Sober, Arthur
Stasko, Tom
Wang, Linda
Wang, Richard
Wong, Mike
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 some 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.