

COSM 2018 4/21 PANEL DISCUSSION

“R.I.P. RRP: “What Lies Ahead for Advanced RRP”

Moderator - Dr. Garrett (Vanderbilt)

Panelists - Dr. Craig Derkay (E. Va. Med. School), Dr. Simon Best (JH), Dr. Clint Allen (NIH/JH)

1) Dr. Derkay - Background and an overview of treatments for advanced RRP:

Diagnosis Age Spectra –

“Three Peaks”, i.e. juvenile, mid 30s and 60s that have been seen when analyzing RRP diagnosis age information. Data provided came from:
Age of onset of recurrent respiratory papillomatosis: a distribution analysis, Volume #1, Issue 5, Pages 448-453, First Published: 13 October 2015: DOI 10.1111/cos.12565

How often does RRP spread outside of the larynx?

- subglottis/tracheal/pulmonary ~ 15-30% (Kashima)
- pulmonary ~ 5% (Derkay)
- tracheal, pulmonary tree ~ 13% (Schraff: 94/700)

Issues with RRP spread outside of the larynx?

- Tracheo-bronchial complications include: pneumonia, tracheal stenosis, lung abscess, pneumatocele, empyema
- Cavitory lesions: central area of necrosis with A/F level on imaging
- Malignant transformation most common with pulmonary spread (Considered most significant risk factor for mortality from RRP)
- **Can we prevent this disease before it gets this bad?**

Can Gardasil HPV vaccination help prevent/slow recurrence of existing RRP?

- Gardasil is designed as an HPV/Cancer preventative vaccine, but there is a suggestion from 9 of 12 studies to support some effectiveness against existing RRP recurrence.
- Following prospective study in Australia (where there is more than 80% Gardasil vaccination compliance) positive impact is already being seen with only 15 new RRP cases in last 5 years.

Immunologic responses to a novel DNA vaccine targeting HPV-11 E6E7:

Ahn J, et al.(... S. Best), Laryngoscope 2017

- Preclinical investigation in C57BL/6 mice
- DNA vaccine encoding the HPV 11 E6/E7 genes was linked to calreticulin (protein that in humans is encoded by the CALR gene.)
- Immunologic response measured by vaccinating mice and measuring CD8 +Tcell responses
- A tumor cell line containing HPV 11 E6/E7 was created and the novel DNA vaccine ability to control tumor growth measured in vivo

- Vaccinated mice had a significantly lower tumor growth rate and smaller tumor volumes.
- Promising strategy for treating RRP

Xenograft model for therapeutic drug testing in RRP

Ahn J., et al. (... S. Best). Annals 2015

- Serial xenografting of human pulmonary papilloma in immunocompromised mice designed for in vivo drug testing. A dramatic therapeutic response was observed with drug testing using Avastin (bevacizumab).
- Extension of research done at Georgetown to identify specific drug sensitivity for an individual patient's papilloma.
- Future goal is "personalized medicine", i.e., customize treatments for individual patients.

Genetic susceptibility of RRP to adjuvant therapy

Core grant approved by AAO-HNS: David Lee, Cincinnati

- Design: Whole genome sequencing (WGS) and establishing a conditionally reprogrammed cell-culture system for the purposes of characterizing genetic and transcriptional aberrations and testing therapies for individualized treatment of children with RRP.
- Long term goal: to define the genomic aberrations in detail using WGS, global transcriptomics, and metabolomics in order to identify patient specific mutations and alterations in transcriptional and small metabolite fingerprints.
- Builds on work initiated by Farrel Buchinsky and Dick Schlegel.

2) Dr. Simon Best - Systemic Avastin Use in RRP:

- Dr. Best presented on eight patients currently using systemic Avastin for the treatment of aggressive RRP, including tracheal and pulmonary.
- All but one patient had pulmonary disease.
- Other prior therapies included cidofovir, interferon, celecoxib, DIM.
- Prior to administration of systemic Avastin, surgery intervals ranged from every three weeks to once a year.
- Every patient reported at least a partial response, with laryngeal and tracheal sites seeing the greatest level of reduction, in most cases complete reduction of disease.
- Pulmonary disease remained stable or reduced.
- One patient went from every three week interventions to every three months (stenosis noted). Among other patients with pre-treatment intervals ranging from 2 to 3 months, one went to every four months and five went to no surgical intervention needed.
- Presently, Dr. Karen Zur has 6 patients on this therapy and Dr. Simon Best has 4 patients on this therapy.

Best practice recommendations for IV Avastin:

- Partner with Medical Oncology
- Approval obtained on a case by case basis (Dr. Best noted they are not having issues with insurance approval.)
- Side effects that require monitoring include, hypertension and renal function.
- No hair loss expected as it is a VEGF receptor blocker.
- Debridement in OR, immediately followed by first IV dose within a couple of days (no additional benefit to sublesional injections).
- Dose at 10mg/kg IV, with starting frequency q3 weeks
- Second look in OR at 3-6 weeks, debridement as needed to maximize window for medication to work. (Of note, many centers will do a CT after first three doses-especially in pulmonary patients, but recommendation is on pulmonary CT at q6 months due to pulmonary having a slower response.)
- Laryngeal and tracheal disease respond very quickly (as soon as second dose).
- After 4-5 doses, interval between doses can be lengthened slowly
 - (Q6 weeks-q9 weeks-q12 weeks)

3) Dr. Clint Allen - Harnessing Immunity to Fight RRP

- Dr. Allen presented on the trial at the NIH, Bethesda, MD, using Avelumab. Due to restrictions on this trial being in the final stages of publication, he was only allowed to release two slides related to the study, but provided an excellent background on the immunology process that was used to gain approval for this trial.
 - Paradigm of specific adaptive immunity:
 - HPV Infected Cells (tumor cells) -> pre-apoptotic cells -> dying cells (tumor antigen processed by antigen presenting cells (APCs)->macrophage and dendritic phagocytosis (immune response phase)->lymph node activated->total exposure and activation->(antigen specific T-lymphocytes are activated and respond)->tumor specific T-cells->(antigen specific T-lymphocytes eradicate antigen-presenting target tumor cells)->tumor cells
- 2/3 of head and neck cancers display evidence of a T-cell inflamed response
- Expression of immune checkpoints in the tumor can turn off infiltrating T-cells
- About 80% of all head and neck cancers are positive for expression of PD-L1 (seiwert et al. Lancet Oncol 2016 PMID:27247226)
- RRP is antigenic and immunogenic

- (The presence of HVP type 6/11 ensures the presence of antigen for T-cells to target. RRP lesions demonstrate CD8 T-cell infiltration and PD-L1 expression)
- Preliminary results from Phase II trial treating RRP with Avelumab (this is all trial was allowed to release on this date)
- 12 patients, 5 female/7 male, mean age 45 (22-64), baseline anatomic Derkay score mean 15 (10-26).
- Of patients with measurable laryngeal disease, 8/11 (72.7%) had reduction in anatomic Derkay score of >30% (defined partial response) after 3 doses (6 weeks) of Avelumab.
- Of patients with measurable lung disease, 0/4 (0%) had reduction in size of lesions of >30% (defined partial response).
- No grade $\frac{3}{4}$ immune-related adverse events from Avelumab treatment
- Plans for future-we are going to conquer RRP (Upcoming trials-NIH)
- Avelumab conjugated to a TGFb trap-block PD pathway and eliminate TGFb concurrently-open in next 2-3 months.
- We are currently trying to close a T-cell receptor that specifically recognizes HPV-11 so we can offer adoptive transfer cell therapy for patients with the most severe HPV-11+ pulmonary RRP.

Some key highlights of this RRP panel discussion were the results from the systemic Avastin study and the detailed information about new directions of immunotherapeutic treatments presented by Dr. Allen.