New Era of Precision Medicine for Head and Neck Cancer

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Disclosures

I have no disclosures.
Which treatment offers our patients the best chance for cure with the least treatment-related morbidity?
Clinical Trials and Biomarkers

HPV Epidemic

Immunotherapy

Precision Medicine
Clinical Trials and Biomarkers

HPV Epidemic

Immunotherapy

Precision Medicine
Clinical Trials and Biomarkers

Can response to a single cycle of induction chemotherapy predict the ability to cure larynx cancer with chemoradiation?
University of Michigan Clinical Trial for Advanced Larynx Cancer

Induction Chemotherapy

Responders → Chemoradiation

Non-Responders → Laryngectomy + XRT

87% 3-year survival rates

This approach allowed us to cure the cancer while preserving the larynx in 71% of patients.
Improved Survival Compared to Historic Control

U-M Larynx Trial

VA Larynx Trial

Log-Rank Statistics=8.053  df = 1  p=0.0045

VA268  UMCC9520

UMCC9520 : (n=)  (63)  (39)  (26)  (15)  (8)  (4)  (2)
VA268 : (n=)  (166)  (146)  (119)  (96)  (84)  (74)  (67)
Larynx Tumors with High Bcl-xL are Cisplatin-Resistant (Bcl-xL blocks programmed cell death)

Kumar B et al, Archives of Otolaryngol 2007

Rate of Larynx Preservation

Time of Laryngeal Preservation

? opportunity to target Bcl-xL
(-)-Gossypol (AT101)

- Component of ancient Chinese herbal medicine derived from cottonseeds
- Binds to BH3 pocket of Bcl-xL and blocks anti-apoptotic effect
- Efficiently targets cisplatin-resistant tumor cells for apoptosis \textit{in vitro} and \textit{in vivo}

Collaboration with Shaomeng Wang; AT-101 lead compound in Phase II Trials with Ascenta Therapeutics

Oliver C et al Clinical Cancer Research 2004
Bauer J et al Molec Cancer Ther 2005
This clinical trial is designed to test whether AT101 decreases the need for laryngectomy by improving response to a single cycle of induction chemotherapy.

TP = Docetaxel and Platinum

CR = complete response
PR = partial response
NR = no response
Clinical Trials and Biomarkers

Which patients will benefit from surgery for advanced oral cavity/oropharynx cancer?
We used a single cycle of induction chemotherapy to stratify patients for chemoradiation versus surgery/XRT

Worden F et al. JCO, 2008
Kumar B et al. JCO, 2008
The results were much better in oropharynx cancer than in oral cavity cancer.
HPV is a Favorable Biomarker for Survival in Oropharynx Cancer

HPV in situ hybridization

p16 Expression: a Surrogate for HPV

\[ p16 = \]

\[ p = \leq 0.0001 \]
The New University of Michigan Paradigm for Oropharynx Cancer

- Carboplatin/docetaxel/intensity modulated radiation IMRT spares contralateral parotid gland and pharyngeal constrictors
- Excellent local/regional control and survival
- Improved swallowing results
Oropharynx Cancer Clinical Trial Design

**Registration**
- Tumor Staging
- Molecular Markers
- Imaging QOL

**Endoscopy**

**IMRT + Weekly:**
- Carboplatin AUC 1
- Paclitaxel 30 mg/m²

**EVALUATION**
- 12 weeks

**Salvage Surgery**

**Follow Up**

Median Follow-up Time: 36 months (95% CI [31,39] mo)
Intensity Modulated Radiation Therapy

- Can target tumor more precisely
- Can spare adjacent normal tissues, like pharyngeal constrictors and reduce toxicity
- Better swallowing outcomes

Feng, F et al., J Clin Oncol 2010
Results for Chemoradiation for Stage III/IV Oropharynx Cancer

- 73 patients
- Excellent survival rates
- 96% local regional control
- Dysphagia was absent or minimal in 95%

Feng, F et al., J Clin Oncol 2010
Biomarkers and Clinical Trials

HPV Epidemic

Immunotherapy

Precision Medicine
High-risk Human Papillomaviruses: A Highly Contagious Cause of Cancer
Two distinct diseases comprise OPSCC

- p53 mut
- p16
- 3p, 4q, 5q, 8p, 13q del

- HPV
  - E7
  - E6
  - p53
  - p16
  - pRB
• Michael J. Douglas disclosed that he was diagnosed with a T4N2bM0 HPV-related throat cancer in 2011. He is a former smoker.
• He spoke at the 2014 American Head and Neck Cancer Society Meeting as a keynote speaker
• He received chemoradiation and remains free of evidence of disease

Photo taken June 4, 2016 at Jatin Shah’s Festschrift and Celebration
HPV-related Oropharynx Cancer is a Sexually Transmitted Disease

- Oropharyngeal cancer risk is increased with
  - High lifetime number of sexual partners (3.1 odds ratio)
  - High lifetime number of oral-sex partners (3.4 odds ratio)
  - Marijuana use

Which head and neck cancers are likely to be HPV-related in U.S.A.?

- Nasopharynx: HPV-related in 30% of cases
- Oropharynx: HPV-related in 90% of cases
- Oral cavity, larynx, and hypopharynx: HPV-related in 5% of cases
HPV is a Favorable Prognostic Marker in Many Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cases</th>
<th>Marker</th>
<th>Survival</th>
<th>First author, year</th>
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</thead>
<tbody>
<tr>
<td>RTOG 0129</td>
<td>323</td>
<td>HPV</td>
<td>82% vs. 57% (3-year)</td>
<td>Ang, 2010</td>
</tr>
<tr>
<td>TROG 02.02</td>
<td>185</td>
<td>p16$^{\text{INK4A}}$</td>
<td>91% vs. 74% (2-year)</td>
<td>Rischin, 2010</td>
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<tr>
<td>DAHANCA 6/7</td>
<td>794</td>
<td>p16$^{\text{INK4A}}$</td>
<td>66% vs. 28% (5-year)</td>
<td>Lassen, 2011</td>
</tr>
<tr>
<td>TAX 324</td>
<td>111</td>
<td>HPV</td>
<td>82% vs. 35% (5-year)</td>
<td>Posner, 2011</td>
</tr>
</tbody>
</table>
Future Directions

• Future clinical trials should address whether treatment for HPV-positive, non-smoking patients can be de-intensified to limit morbidity of treatment without affecting success of treatment and role of transoral approaches in cohort.

• Similarly, trials should address whether intensification of treatment and/or surgical intervention for HPV-negative smoking patient can effect better survival.
Role of HPV Vaccination

- Gardasil, quadrivalent (types 6, 11, 16, 18) vaccine, recombinant
- Indicated for use in young women and men age 9-26
- Vaccine is highly likely to prevent the development of HPV-related head and neck cancer
- Will take at least 30 years for vaccination strategy to impact incidence of throat cancer
Biomarkers and Clinical Trials

HPV Epidemic

Immunotherapy

Precision Medicine
PD-1/PD-L1 Inhibitors Overcome Local Immunosuppression

- PD-1: programmed cell death inhibitor 1 present on T cells
- When PD-1 binds to its ligand, PD-L1 (on tumor cells), the ability of the T cell to produce an effective immune response is down-regulated

Nivolumab and Pembrolizumab are PD-1 antibodies that show remarkable and durable anti-tumor activity in certain malignancies
Among patients with platinum-refractory, recurrent squamous-cell carcinoma of the head and neck, treatment with nivolumab resulted in longer overall survival than treatment with standard, single-agent therapy. (CheckMate 141).

Ferris R et al. NEJM Oct 2017

“tail on the curve” is an important observation.
Biomarkers and Clinical Trials

HPV Epidemic

Immunotherapy

Precision Medicine
Medicine of the Present: One Treatment Fits All
Medicine of the Future: Personalized Diagnostics and Therapies
Mi-Oncoseq Schema: Recurrent/Refractory Tumor Patient

- Recurrent Tumor Patient
- Whole Genome Screen
- Targeted Therapeutic Clinical Trials

Genes of Interest:

- HPV
- NOTCH
- Cyclin D1
- p53
- mTOR
- P13K
Precision Medicine Case Study #1

• D.R. is a pediatrician who presented with highly aggressive sarcoma of the mandible.
• Distant metastasis were present at diagnosis
• Tumor progressed despite aggressive XRT and chemotherapy and frequent debulking
Precision Medicine Case Study #1
Applying the Mi-Oncoseq Schema

- Patient enrolled in Mi-Oncoseq
- No “druggable targets” identified
- Patient diagnosed with Lynch syndrome, familial colon cancer and sarcomas
- Family members actively screened for malignancies
Mi-OTOseq Schema: Newly Diagnosed Tumor Patient

Newly Diagnosed Tumor Patient → Whole Genome Screen

Whole Genome Screen → Future Targeted Therapeutic Clinical Trials

Genes: mTOR, HPV, NOTCH, Cyclin D1, p53, P13K
Precision Medicine Case Study #2

- Young woman; non-smoker, non-drinker, HPV-negative recurrent tongue cancer (predicted to be a less genetically complex patient)
- Amplification of FGFR1 on chromosome 8

If patient should relapse, she could be enrolled in a clinical trial with an FGFR inhibitor

Western blot shows FGFR1 overexpression in HNSCC_1
MiOTOSeq Progress To Date

- 67 patients enrolled
- Linked with all ongoing clinical trials
- 250 related or actionable genes in panel
- Matched circulating tumor DNA monitoring on all patients
Numerous Gene Alterations Identified in Head and Neck Cancers

<table>
<thead>
<tr>
<th>Gene Amplification</th>
<th>Mutation</th>
<th>Insertion/Deletion Frameshift</th>
<th>Stop Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53/MDM</td>
<td>NOTCH1</td>
<td>FBXW7</td>
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<tr>
<td>NOTCH</td>
<td>GLI/S</td>
<td>Cell Cycle</td>
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<tr>
<td>CDKN2A</td>
<td>CCND1</td>
<td>CCNE1</td>
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<td>CDK4</td>
<td>CDK5</td>
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<tr>
<td>CHEK2</td>
<td>FGF/FGFR</td>
<td>FGFRI</td>
<td></td>
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<tr>
<td>PIK3CA/PTEN/mTOR</td>
<td>EGFR</td>
<td>ERBB2</td>
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<tr>
<td>ABL1</td>
<td>FLT3</td>
<td>MET</td>
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**FFPE Tumors Characterized with Precision Panel**
We are at the forefront of personalized therapy where we can and must deliver the \textbf{RIGHT} treatment for the \textbf{RIGHT} patient at the \textbf{RIGHT} time
Acknowledgements

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