Hematology/Oncology PRN Focus Session—Confronting the Global Epidemic of Human Papillomavirus (HPV) and Associated Malignancies

Activity Number: 0217-0000-15-128-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Monday, October 19, 2015
3:15 p.m. to 4:45 p.m.
Continental Ballroom 6

Moderator: David L. DeRemer, Pharm.D., BCOP
Clinical Associate Professor, PGY-2 Oncology Residency Program Director, University of Georgia, Augusta, Georgia

Agenda

3:15 p.m. Human Papillomavirus Vaccine Efficacy: Aligning Expectations with Reality
Joel Palefsky, M.D.
Professor of Medicine, Department of Infectious Diseases, University of California, San Francisco School of Medicine, San Francisco, California

3:45 p.m.

3:45 p.m. Prevention and Treatment - A Focus on Cervical Cancer
Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP
Associate Professor & Director of Women's Health Integrative Medicine Research Program, Department of Obstetrics, Gynecology & Reproductive Sciences, University of Texas Medical School at Houston, Houston, Texas

4:15 p.m. HPV Positive Oropharyngeal Cancer: Is it Time for De-escalated Treatment?
Sarah L. Scarpace, Pharm.D., MPH, BCOP
Associate Professor, Albany College of Pharmacy and Health Sciences; Clinical Pharmacy Specialist, St. Peter’s Health Partners Cancer Care Center; Albany, New York

Conflict of Interest Disclosures
David L. DeRemer: Speaker’s bureau for Merck.
Joel Palefsky: Consultant/member of advisory board for Merck and Co., Hera Therapeutics, The Vax; Clinical investigator for Merck and Co., Hologic; Received grant funding from Merck and Co., Hologic, and Pharmajet.
Sarah L. Scarpace: Speaker’s bureau for Eli Lilly, Pfizer, and Merck.
Judith A. Smith: Received grant funding from Amino Up Chemical, LTD.

Learning Objectives

1. Discuss the clinical development and impact on global utility of HPV vaccines.
2. Compare and contrast expectations and limitations of HPV vaccination.
3. Describe contemporary barriers for implementing HPV vaccinations into clinical practice in both the United States and developing countries.
4. Describe the pathogenesis and current treatment options for cervical cancer.
5. Review ACIP guidelines for HPV vaccinations.
7. Discuss pathophysiology and molecular signatures of HPV-positive oropharyngeal cancer.
8. Compare and contrast clinical response of HPV positive oropharyngeal cancers compared with those that are HPV negative.
9. Evaluate emerging data utilizing de-escalated treatment strategies for HPV-positive oropharyngeal cancers.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/gc15
Human Papillomavirus Vaccine Efficacy: Aligning Expectations with Reality

Joel Palefsky
Department of Medicine
University of California, San Francisco

Disclosures
- Merck and Co- study investigator, research grant and travel support, advisory boards
- Pharmajet- research support
- Hologic- research grant support
- The Vax- SAB
- Hera Therapeutics- SAB

Take-home points
- HPV vaccines are very efficacious
- HPV vaccines are very safe
- HPV vaccine programs are challenging to implement in developed countries
- HPV vaccines are costly in developing countries and challenging to implement

Objectives
- Discuss the clinical development and impact on global utility of HPV vaccines
- Compare and contrast expectations and limitations of HPV vaccination
- Describe contemporary barriers for implementing HPV vaccinations into clinical practice in both the United States and developing countries

HPV-related cancers

<table>
<thead>
<tr>
<th>Average no. of cases/person (age-associated cancers)</th>
<th>Cancer attributable to any HPV</th>
<th>Cancer attributable to HPV16/18</th>
<th>Average no. ( \times 10^3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>6.00</td>
<td>1.20</td>
<td>0.60</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2.56</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.52</td>
<td>0.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Cervix</td>
<td>1.20</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Anal Vagina</td>
<td>0.10</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Vulva</td>
<td>0.05</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Oropharynx materials of head and neck</td>
<td>0.02</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Other cervical cancer of head and neck</td>
<td>0.01</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>15.711</td>
<td>3.146</td>
<td>1.5713</td>
</tr>
</tbody>
</table>

MMWR / August 29, 2014 / Vol. 63 / No. 5
HPV Infection and Productive Life Cycle

Virus introduced through microabrasion

Viral DNA replication

Virion assembly

Late HPV protein production L1 & L2

Infectious virions shed

Virus infection

Early HPV protein production E1, E2, E4, E5, E6, & E7

HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis

L1 gene of HPV DNA

Empty viral capsid (VLP)

Transcription

mRNA translation

Capsid proteins

Infects immune response in host

Eukaryotic cell

HPV L1 gene inserted into a plasmid

Spectrum of HPV disease

Morphologic Continuum

LSIL

HSIL

Prophylactic efficacy of quadrivalent vaccine (qHPV) CIN & AIS

Per-Protocol Population (Protocols 007, 013, and 015) Mean Follow-Up - 44 months

<table>
<thead>
<tr>
<th>Endpoint**</th>
<th>qHPV Cases (N = 9075)</th>
<th>Placebo Cases (N = 9075)</th>
<th>% Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18-related CIN or AIS</td>
<td>9</td>
<td>225</td>
<td>96</td>
<td>(92, 100)</td>
</tr>
<tr>
<td>By Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6-related</td>
<td>0</td>
<td>47</td>
<td>100</td>
<td>(92, 100)</td>
</tr>
<tr>
<td>HPV 11-related</td>
<td>0</td>
<td>12</td>
<td>100</td>
<td>(65, 100)</td>
</tr>
<tr>
<td>HPV 16-related</td>
<td>8</td>
<td>137</td>
<td>94</td>
<td>(89, 98)</td>
</tr>
<tr>
<td>HPV 18-related</td>
<td>1</td>
<td>41</td>
<td>98</td>
<td>(91, 100)</td>
</tr>
<tr>
<td>By Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN 1</td>
<td>7</td>
<td>170</td>
<td>96</td>
<td>(91, 98)</td>
</tr>
<tr>
<td>CIN 2/3</td>
<td>2*</td>
<td>110</td>
<td>98</td>
<td>(93, 100)</td>
</tr>
<tr>
<td>AIS</td>
<td>0</td>
<td>7</td>
<td>100</td>
<td>(81, 100)</td>
</tr>
</tbody>
</table>

*Subjects are counted only once per row, but may be in more than one row

Prophylactic efficacy of quadrivalent vaccine (qHPV) External Genital Lesions

Per-Protocol Population (Protocols 007, 013, and 015) Mean Follow-Up - 44 months

<table>
<thead>
<tr>
<th>Endpoint**</th>
<th>qHPV Cases (N = 9075)</th>
<th>Placebo Cases (N = 9075)</th>
<th>% Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18-related Ext Gen Lesion</td>
<td>2</td>
<td>227</td>
<td>99</td>
<td>(97, 100)</td>
</tr>
<tr>
<td>By Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6-related</td>
<td>2</td>
<td>179</td>
<td>99</td>
<td>(94, 100)</td>
</tr>
<tr>
<td>HPV 11-related</td>
<td>0</td>
<td>36</td>
<td>100</td>
<td>(89, 100)</td>
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<tr>
<td>HPV 16-related</td>
<td>0</td>
<td>46</td>
<td>100</td>
<td>(72, 100)</td>
</tr>
<tr>
<td>HPV 18-related</td>
<td>0</td>
<td>13</td>
<td>100</td>
<td>(68, 100)</td>
</tr>
<tr>
<td>By Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Warts</td>
<td>2</td>
<td>193</td>
<td>99</td>
<td>(94, 100)</td>
</tr>
<tr>
<td>VIN 1 or VaIN 1</td>
<td>0</td>
<td>28</td>
<td>100</td>
<td>(86, 100)</td>
</tr>
<tr>
<td>VIN 2/3 or VaIN 2/3</td>
<td>0</td>
<td>23</td>
<td>100</td>
<td>(83, 100)</td>
</tr>
</tbody>
</table>

*Subjects are counted only once per row, but may be in more than one row

The nonavalent HPV vaccine

The nonavalent HPV vaccine


The nonavalent HPV vaccine

MMWR / March 27, 2015 / Vol. 64 / No. 11; Joura E et al


Quadrivalent vaccine in males: efficacy against HPV 6/11/16/18-related AIN and anal cancer in MSM

Palefsky J, Giuliano et al. NEJM 2011, 365: 1576-85

Cost effectiveness


Safety of nonavalent vaccine


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**Cost effectiveness**

**Conclusions: Cost-effectiveness**
- Primary 9vHPV for both sexes is likely cost-saving compared to 4vHPV for both sexes
  - Results consistent across, within models
  - Cost per QALY < $0 in most scenarios
    - < $25,000 in all sensitivity analyses


**ACIP recommendations for HPV vaccine in women**
- 9vHPV, 4vHPV or 2vHPV can be used for:
  - routine vaccination of females aged 11 or 12
  - females through age 26 years who have not been vaccinated previously or who have not completed the 3-dose series
  - If providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18

**ACIP recommendations for HPV vaccine in men**
- 10/11- qHPV/nHPV approved for routine use in boys and men age 9-21 years to prevent HPV 6/11-related genital warts and anal HPV infection, AIN and anal cancer due to vaccine types
- Approved for use (permissive) in men age 22-26
- Approved for routine use in men age 22-26 if immunosuppressed or MSM

**Post-approval vaccine efficacy**
- Girls and women, with high female vaccination coverage (>50%)
- Boys and men, with high female vaccination coverage (>50%)
- Girls and women, with low female vaccination coverage (<50%)
- Boys and men, with low female vaccination coverage (<50%)


**Safety of nonavalent vaccine**
- The Vaccine Adverse Event Reporting System (VAERS)
- The Vaccine Safety Datalink (VSD)
- The Clinical Immunization Safety Assessment (CISA) Network
Safety of nonavalent vaccine


Challenges- uptake

- Very expensive- $130 or $140 per dose
- $5/dose GAVI and PAHO

Challenges- cost

- HPVs vaccines are very efficacious
- HPVs vaccines are very safe
- HPVs vaccine programs are challenging to implement in developed countries
- HPVs vaccines are costly in developing countries and challenging to implement

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4595496/#t6hash.3zo.jsn7P_dipd, accessed 9/18/15

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Solutions

- HPV vaccine programs are challenging to implement in developed countries
  - School-based vaccination
  - Two-dose vaccination
  - Needle-free vaccination
- HPV vaccines are costly in developing countries
  - Two-dose (or one dose?)
  - New cheaper vaccines?
  - Intra-dermal reduced dose?

Thank you!
**Conflict of Interests**
- I have received unrestricted research funding from the following companies in the past 12 months but all unrelated to research being presented today:
  - Janssen Pharmaceuticals
  - Astellas
  - Marinova, LTD

**Human Papillomavirus (HPV)**
- Non-enveloped dsDNA virus
  - Infects epithelial and mucosal surfaces.
- HPV is a very common viral infection
  - 230 subtypes of HPV that have been identified,
  - one hundred human subtypes
- HPV causes plantar warts
- 30-40 strains can infect epithelial lining of ano-genital tract
  - HPV 6 causes anogenital warts
- Fifteen of the human HPV subtypes are carcinogenic
  - The most common subtypes: HPV 16, 18, 31, 39, and 41
    - HPV appears to be an important co-factor in the development of dysplasia and cancer
    - It does not cause either condition by itself

**Learning Objectives**
- Understand the role of HPV as a co-factor in the development of cancer.
- Describe the impact of chronic viral infections on host immunity.
- Discuss potential role of AHCC as a treatment option for eradication HPV Infections
- Explain the diagnosis, prognosis and treatment of cervical cancer

**HPV Infection**
- Virus transmitted via direct contact
  - Invades upper layers of epithelium
  - First linked to cervical cancer risk
  - Also associated with 15% H&N cancers

Impact of HPV Worldwide

80 percent of the cases occur in developing countries

2nd leading malignant neoplasm in women

Accounts for most cancer deaths in women

Major public health problem in 3rd world countries

Risk Factors

- Increased HPV exposure
  - First intercourse at early age
  - Multiple partners
  - H/O other sexually transmitted diseases
  - Intercourse with uncircumcised males
- Decreased screening
- Low socioeconomic status
- Poor access to health care
- Smoking
- HIV/AIDS
- Oral contraceptive use/multiple pregnancies

Human Papilloma Virus

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Risk</th>
<th>Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>6, 11</td>
<td>Low</td>
<td>Present in 90% of genital warts</td>
</tr>
<tr>
<td>16</td>
<td>High</td>
<td>Present in 50% cervical cancers</td>
</tr>
<tr>
<td>18, 33, 35, 39, 45, 51, 52, 56, 58, 68, 73, and 82</td>
<td>High</td>
<td>Present in 20% of cervical cancers</td>
</tr>
<tr>
<td>31, 33, 35, 39, 45, 51, 52, 56, 58, 68, 73, and 82</td>
<td>High</td>
<td>Present in 30% of cervical cancers</td>
</tr>
<tr>
<td>40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>


Societal Impact

- 80 percent of the cases occur in developing countries
- 2nd leading malignant neoplasm in women
- Accounts for most cancer deaths in women
- Major public health problem in 3rd world countries

What is the immune system

- Body’s natural defense
  - Identification of self vs. foreign molecules
  - Immune response
    - Fight pathogens
      - Prevent infection
  - Innate Immunity
    - First line of defense
      - Barriers
        - Skin
        - Mucous membranes
      - Environment
        - Body temperature
        - pH
      - White blood cells
        - Neutrophils
        - Inflammatory response

Immune response
Immune Response

- Adaptive Immunity
  - Activated
    - when innate immunity fails
    - Recall exposure to pathogens
  - Targeted response
  - Receptor – mediated
    - Antibodies (B cell receptors)
    - Major Histocompatibility Complex (MHC) (T-cell receptors)

Duration of HPV infection

- 608 female college students (age 17–23)
  - Cervicovaginal cells obtained for HPV typing at each (every 6 mo) visit
  - Median duration of infection 8 months
  - 60% HPV infected during study
  - Average incidence of HPV 14%
  - Probability of resolving infection decreases
    - 3% after first 6 months
    - 3% after second six months
    - 11% after third six months

Immune System Overview

<table>
<thead>
<tr>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of immune response</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Time of immune response</td>
<td>Response within minutes</td>
</tr>
<tr>
<td>Duration of immune response</td>
<td>No memory</td>
</tr>
<tr>
<td>Immune component activated</td>
<td>Natural barriers, phagocytes</td>
</tr>
</tbody>
</table>

Cellular Immune Response

www.biologymad.com
Progression to Cancer

HPV and cancer

- HPV DNA has been detected
  - 99% of cervical cancers
  - 95% of anal cancers
  - 60% of oropharyngeal cancers
  - 65% of vaginal cancer
  - 35% of penile cancer

- There is no cure for HPV infections
  - Prevention by vaccination
  - Detection by Pap smear for cervical cancer
  - No current treatment for infection
  - Topical treatments of HPV related genital warts

AHCC and Cancer

- Reduce side-effects of chemotherapy
  - Reduce toxicity
  - Improve quality of life

- May improve treatment outcomes
  - Research supports the following modes of action:
    - Increases Tumor Necrosis Factor
    - Increases Gamma Interferon
    - Increases IL-12 (all decrease when undergoing chemotherapy)
    - Decreases circulating level of IAP (Immuno-suppressive acidic protein)
    - Decreases circulating level of IAP and TGF-B (tumor growth factor–Beta)

- Recommended therapeutic dose: 3g daily

Active Hexose Correlated Compound (AHCC)

- Prepared from cultured mycelium of a Basidiomycetes
  - Main component of AHCC is acetylated α-glucan

Summary Metabolism Profile of AHCC

<table>
<thead>
<tr>
<th>Metabolism Pathway</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
<th>No. Reactions</th>
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</thead>
<tbody>
<tr>
<td>Glu4H6 Pnt4</td>
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<td>Glu4H6 Pnt4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

www.ahccresearch.com
AHCC- HPV Pre-clinical Studies

Summary

**In vitro studies**
- Confirmed eradication of HPV
  - Dosed with AHCC 42 mg/mL every 24 hours for 7 days
  - Achieved HPV negative after 24 hours
  - Followed by 7 days of no treatment
  - Confirmed HPV negative

**In vivo studies**
- HPV 16+/18+ expression was eradicated with once daily AHCC (50 mg/kg) dosing for 90 days
  - Confirmed durable response after 30 day observation with no treatment.
  - Repeated study above to evaluate mechanism of AHCC eradication of HPV
  - Confirmed HPV eradication
  - Modulation of interferon beta/alpha/gamma and IgG
  - Evaluated in cervical cancer treatment model (HPV 16+/18+ and HPV- models) AHCC + cisplatin compared to cisplatin alone
  - Confirmed HPV eradication
  - Observed improved cisplatin activity in both tumor models

Study Objectives

- Evaluate the efficacy of active hexose correlated compound (AHCC) to eradicate HPV infections in women with HPV positive/negative cytology PAP smears.
- Define the duration of therapy of AHCC required for treatment of HPV infections.
- Determine the durability of response to active hexose correlated compound (AHCC).

Animal study results

Daily dose x 90 days + 30 days observation

Previous Prevention Study Animal Study Results

Daily dose x 90 days + 30 days observation

Inclusion Criteria

- Women over 30 years of age who have a HPV positive test and normal/negative cytology, atypical cells, ASCUS, or CIN1 or CIN2 cervical dysplasia within three months of study entry.
- Women must have had another HPV positive test with normal/negative cytology within no less than 6 months and no more than 18 months prior to study entry.
  - This is to help establish persistent HPV infection
- Negative urine pregnancy test within 7 days of therapy start.
- Women must have adequate hematologic, renal, and hepatic function: ANC >/= 1,500 cells/mm3, platelets 100,000 >/= cells/mm3; Creatinine clearance >/= 60 mL/min (estimated by Cockcroft Gault equation), total bilirubin, SGPT, SGOT, and alkaline phosphatase </= 1.5 times normal.
- Patients must sign an approved informed consent indicating that they are aware of the investigational nature of this study.
- Patients must agree to return to clinic for repeat HPV+ testing and complete medication administration calendar.

Exclusion Criteria

- History of myocardial infarction within past 6 months, unstable angina, CHF, or uncontrolled hypertension (> 140/90).
- Women with a current or prior diagnosis of cancer.
- Women with a current diagnosis of CIN3 cervical dysplasia
- Women that are pregnant or breast feeding.
- Women with a history of Hepatitis (autoimmune, A, B, or C) or antigen positive.
- Patients with history of significant psychiatric disorders (schizophrenia, bipolar, psychosis) or uncontrolled seizures.
- Patients with significant medical co-morbidities at the discretion of the primary Gynecologist, including immunosuppressive conditions (i.e. HIV+, rheumatoid arthritis, etc) or taking immune modulation medications (i.e. immunosuppressants)
- Patients who have undergone a hysterectomy (supracervical hysterectomy allowed)
Study Design

Treatment

- Initial:
  - AHCC 3 grams once daily with or without food
  - Weekly HPV testing x 5 weeks
  - Stopped with first negative result
- Final Amendment:
  - AHCC 3 grams daily without food
  - Monthly HPV testing
  - Stopped with first negative result
- Second Amendment:
  - AHCC 3 grams daily without food
  - Monthly HPV testing
  - Continue AHCC minimum of three months
    - At least one month after first negative result
- Final Amendment:
  - AHCC 3 grams daily without food
  - Monthly HPV testing
  - Continue AHCC minimum of three months up to six months
    - At least one month after first negative result

Study Design

Monitoring

- HPV testing:
  - OutReach Laboratory, The University of Texas Health Science Center at Houston Medical School (UT Health)
    - Thin Prep brush sample
  - HPV testing was completed with the Cervista HPV HR Test (Hologic, Inc., Bedford, MA)
- Immunological marker monitoring
  - Core Pharmacology Laboratory, Department of Obstetrics, Gynecology & Reproductive Sciences, UTHealth - The University of Texas Health Science Center at Houston Medical School
  - Blood samples obtained at each visit
    - IgG
    - Interferon (IFN) alpha
    - Interferon (IFN) beta
    - Interferon (IFN) gamma

Results

- A total of ten HPV+ women were enrolled on study.
- Patient Demographics:

<table>
<thead>
<tr>
<th>N=10</th>
<th>Mean (Stdev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.6 (+/-8.8)</td>
</tr>
<tr>
<td>Race</td>
<td>All white</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>2- hispanic/latino 8 non-hispanic/latino</td>
</tr>
<tr>
<td>BMI</td>
<td>26.6 (+/-4.5)</td>
</tr>
<tr>
<td># Sexual Partners</td>
<td>20 (+/-28)</td>
</tr>
</tbody>
</table>

Summary of Response Data

<table>
<thead>
<tr>
<th>Age</th>
<th>Race</th>
<th>BMI</th>
<th># Sexual Partners</th>
<th>Duration of AHCC Supplement</th>
<th>Durable Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>White</td>
<td>25.3</td>
<td>3</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>White</td>
<td>23.1</td>
<td>10</td>
<td>3 months</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>White</td>
<td>27.3</td>
<td>5</td>
<td>6 months</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>White</td>
<td>22.4</td>
<td>15</td>
<td>6 months</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>White</td>
<td>26.4</td>
<td>14</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Note: IFN (g) is Type 1 IFN
  - associated with virulence
  - High levels suppress production of IFN g and NK/T-cell cytotoxic cell immunity

CERVICAL CANCER

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14
**Diagnosis**

- Pap Test
- Biopsy

**Screening**

**Diagnosis**

- Clinically Staged
- May Use:
  - Exam Under Anesthesia (EUA)
  - Cystoscopy/Proctoscopy
  - CXR, IVP
- Positive findings on CT, MRI, PET, USG, FNA or LAG do **NOT** upstage patient
- But may change treatment planning

FNA = fine needle aspiration, LAG = lymphangiogram

**Signs and Symptoms**

- Abnormal and/or postcoital vaginal bleeding
- Malodorous discharge
- Pelvic pain and/or pressure in advanced disease

**Classification of cervical cancers**

- 75% squamous cell
- 15% adenocarcinomas

**Non-invasive squamous lesions**

- Cervical intra-epithelial neoplasia, CIN
  - CIN grade 2 = moderate lesion
  - CIN grade 3 = Carcinoma in-situ, CIS

**Invasive, malignant cells**

- Penetrated basement membrane
- Infiltrated the stroma
- With vascular/lymphatic invasion

Lowndes C. Epidemiol Infect 2006;134;1-12.

**Staging**

- Clinically Staged

**May Use:**

- Exam Under Anesthesia (EUA)
- Cystoscopy/Proctoscopy
- CXR, IVP

**Positive findings on CT, MRI, PET, USG, FNA or LAG do **NOT** upstage patient**

- But may change treatment planning

FNA = fine needle aspiration, LAG = lymphangiogram

**Signs and Symptoms**

**Classifications of cervical cancers**

- IA1
  - Cone or Simple Hyst
- IA2
  - Radical Hyst + PLND
- IB1
  - Radical Hyst + PLND
- IB2-IVB
  - Chemoradiation

Hyst = hysterectomy, PLND = pelvic lymph node dissection

**Treatment**

**Chemoradiation (Stages IB2-IVA)**

- Combination of:
  - Weekly or q3 weekly chemotherapy
  - Daily external beam radiation to total 45 Gy (25 doses)
  - Intracavitary radiation/ALTO x 2 for another 40-45 Gy
  - Chemotherapy thought to act as a radiation sensitizer

ALTO = After loading tandem and ovoids

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Pelvic Recurrence / Persistent Disease
- Radiation if not used in primary treatment
- If recurrence is central after radiotherapy, consider exenteration
- If previously radiated and sidewall involved, consider chemotherapy

Chemotherapy for Recurrent Cervical Cancer
- Agents with activity:
  - Cisplatin
  - Carboplatin
  - Paclitaxel
  - Docetaxel
  - Irinotecan
  - Topotecan
  - Gemcitabine
  - Vinorelbine

Extrapelvic Recurrence
- Chemotherapy
- Palliative radiotherapy
- Surgical resection (Rare)

Cisplatin For Recurrent Cervical Cancer
- Considered most active agent in metastatic or recurrent cervical cancer
- 50 to 100 mg/m² once every 3 week
  - Response Rate is 20 to 30%
  - Increase in dose 50 mg/m² vs. 100 mg/m²
    - RR increase from 21% to 31%
    - No difference in PFS
    - No difference in OS

Carboplatin For Recurrent Cervical Cancer
- Never compared head to head with cisplatin, but generally considered less active
  - Response rate ~15% in recurrent cervical cancer setting
- AUC = 5 generally used once every three to four weeks

Chemotherapy for Recurrent Cervical Cancer
- Palliative role
- Response rates significantly lower in patients previous treated with surgery or radiotherapy
  - Potential hypothesis is decrease blood flow to pelvic region
### Paclitaxel For Recurrent Cervical Cancer

- Clinical trials evaluated both 3-hr vs. 24hr
  - Dose range 170 mg/m² to 250 mg/m²
  - Response Rates 17 to 21%

- Clinical practice:
  - 135 to 175 mg/m² over 3 hours once every 3 weeks

### Docetaxel For Recurrent Cervical Cancer

- Clinical trials evaluated 100 mg/m² once every 3 weeks
  - Response Rates ~13%

- Clinical practice:
  - 75 mg/m² over 1 hour once every 3 weeks
  - 50 to 60 mg/m² once weekly

### Camptothecins Used in Recurrent Cervical Cancer

- **Topotecan**
  - Clinical Trials:
    - 1.2 mg/m² x 5 days once every 21 days
    - Response rates ~18%
  - Clinical Practice:
    - 4 mg/m² weekly
  - Recent new FDA indication:
    - Combination regimen with cisplatin

- **Irinotecan**
  - Clinical Trials:
    - 125 mg/m² once weekly x 3 weeks on, 1 week off
    - 350 mg/m² once every 21 days
    - Response rates 15 to 24%
  - Clinical Practice: (rare)
    - 100 mg/m² once weekly x 3 weeks on, 1 week off

### Cisplatin-based regimens

**GOG 240**

- Paclitaxel 135 mg/m² over 24hr + Cisplatin 75 mg/m² once every 21 days
  - RR ~ 46%
  - Neurotoxicity, myelosuppression, N/V

- Topotecan 0.75 mg/m² days 1, 2, & 3 with cisplatin 50 mg/m² day one only repeated once every 21 days
  - RR ~ 33%
  - Myelosuppression, N/V

- Cisplatin 80 mg/m² on day one with vinorelbine 25 mg/m² days 1 and 8 once every 21 days
  - RR ~ 43.5%
  - Neurotoxicity and neutropenia

Addition of Bevacizumab has been approved by FDA to improve PFS/OS

### Conclusions

- Single agent regimens have been used with response rates 15 to 30%
- Combination regimens have had promising improvement in response rates 30% to 46%
- New directions with combinations and integration of molecularly targeted agents!
Acknowledgements

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2015 ACCP Global Conference on Clinical Pharmacy

HPV Positive Oropharyngeal Cancer: Is it Time for De-escalated Treatment?
Sarah L. Scarpace, PharmD, MPH, BCOP
October 19, 2015

Learning Objectives

- Discuss pathophysiology and molecular signatures of HPV-positive oropharyngeal cancer
- Compare and contrast clinical response of HPV positive oropharyngeal cancers compared with those that are HPV negative
- Evaluate emerging data utilizing de-escalated treatment strategies for HPV-positive oropharyngeal cancers

Context

“HPV status should not be a routine consideration in treatment selection at this time, except for cases of cancer of unknown primary1.”

“HPV status should not be a routine consideration in treatment selection at this time, except for cases of cancer of unknown primary1.”

Risk Factors:

HPV+ vs. HPV- Oropharyngeal

HPV+
- Younger age at diagnosis
- Male
- White
- Higher income
- Regional vs. local disease
- Treated with radiotherapy
- Type 16 associated with increased number oral sex partners and intensity, duration, and joint-years of marijuana exposure

HPV-
- Smoking
- Drinking
- Older Age
- Less than daily tooth brushing
- Increased number of lost teeth

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Epidemiology:
HPV+ vs. HPV- Oropharyngeal

HPV+
- HPV type 16 most prevalent
- 5-year survival not correlated with stage
- Incidence increasing worldwide
  - 225% from 1988-2004 in USA
- Expected to exceed HPV- cases by 2020 in USA

HPV-
- Lower 5-year survival with increasing stage
- Incidence declined 50% from 1988-2004 in USA

Incidence increasing worldwide
- 225% from 1988-2004 in USA
- Expected to exceed HPV- cases by 2020 in USA


Oral HPV 16 Prevalence
- USA general population: 1%
- European general population: 0.8%
- More common in oropharyngeal than other HN subtypes
- USA oropharyngeal cancer: 38.8%
- European oropharyngeal cancer: 30.2%
- Among HPV+ oropharyngeal cancer:
  - Worldwide: 93.1%
  - North America: 95.7%
  - Europe: 90.9%


Pathophysiology

High-risk HPV (e.g., type 16) encodes E6 and E7 (viral oncoproteins) inactivates TP53 and Retinoblastoma tumor suppressor gene disrupts Cell cycle regulation & DNA repair promotes Tumor progression


Molecular Signatures

HPV+
- HPV-driven transformation
- Wild-type p53
- Wild-type p16
- "normal" cyclin D levels
- PIK3CA oncogene mutations
- Loss of TRAF3
- E2F1 amplification

HPV-
- Mutagenic effects of alcohol and tobacco
- Mutated p53
  - Loss of TP53 function
  - Mutated p16
- Amplified cyclin D levels
- CDKN2A inactivation
- 3q26/28 11q13/22 amplification

Deregulation of signalling pathways and transcription factors

HPV+ OROPHARYNGEAL CANCER: PROGNOSIS AND TREATMENT RESPONSE

### HPV+ versus HPV-

### HPV: Response and Survival

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intervention</th>
<th>Response Rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argiris, 2014 (retrospective)</td>
<td>Cisplatin/ paclitaxel v. cisplatin/5-FU or irinotecan/ docetaxel</td>
<td>55% v. 19% (p=0.022)</td>
<td>12.9 months v. 6.7 months (p=0.014)</td>
</tr>
<tr>
<td>Ang, 2010 (retrospective)</td>
<td>Accelerated RT vs. standard RT</td>
<td>No difference</td>
<td>82.4% v. 57.1% (3-yr OS rate) (p=0.001)</td>
</tr>
<tr>
<td>Fakhry, 2009 (prospective)</td>
<td>Carboplatin/paclitaxel  paclitaxel + standard RT</td>
<td>82% v. 55% (after induction; p=0.01) 84% v. 57% (after chemoRT; p=0.007)</td>
<td>95% v. 62% (2-year OS rate) (p=0.005)</td>
</tr>
<tr>
<td>Ragin, 2007 (meta-analysis)</td>
<td>Meta-analysis of 37 studies which reported outcomes based on HPV status by PCR</td>
<td>HR death = 0.85 (95% CI: 0.7-1.0)</td>
<td></td>
</tr>
</tbody>
</table>

### p16: Response and Survival

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intervention</th>
<th>Response Rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argiris, 2014 (retrospective)</td>
<td>Cisplatin/ paclitaxel v. cisplatin/5-FU or irinotecan/ docetaxel</td>
<td>50% vs. 19% (p=0.057)</td>
<td>11.9 months v. 6.7 months (p=0.027)</td>
</tr>
<tr>
<td>Vermorken, 2013 (retrospective)</td>
<td>Cisplatin/5-FU +/- panitumumab</td>
<td>11.7 months v. 8.6 months in panitumumab arm for p16 -, not +, (p=0.0115)</td>
<td></td>
</tr>
<tr>
<td>Ang, 2010 (retrospective)</td>
<td>Accelerated RT vs. standard RT</td>
<td>Not reported</td>
<td>83.6% v. 51.3% (3-year OS rate; p=0.001)</td>
</tr>
<tr>
<td>Lassen, 2009 (retrospective)</td>
<td>Standard RT</td>
<td>58% v. 28% (5-year locoregional control rate; p=0.0005) 62% v. 26% (p=0.0003)</td>
<td></td>
</tr>
<tr>
<td>Rischin, 2010 (Australia) (retrospective)</td>
<td>RT + cisplatin +/- tirapazamine</td>
<td>93% v. 86% (2-year locoregional control rate; p=0.0003) 91% v. 74% (2-year OS rate; p=0.004)</td>
<td></td>
</tr>
</tbody>
</table>

### Considerations

- Improved prognosis only seen consistently with oropharyngeal cancer
- Many studies retrospective or evaluations of banked tumor samples from prior studies
- Other factors affecting prognosis: loss of >5% weight; pack-years of smoking, and TN stage
- Rischin found that only p16 status predicted OS in multivariate model of hemoglobin, TN stage, and ECOG PS
- Anti-EGFR therapy may be more beneficial for p16- patients than p16+
- Rates of distant metastases same for both HPV+/-

### Smoking Still Matters

- p16 positive patients less likely to report >20 pack-year smoking history
- Risk of progression or death increases by 1% per pack-year, regardless of p16 status
- Risk of death doubles if smoke during RT

### Data and Recommendations

DE-ESCALATED THERAPY
De-escalation: Why?

- HPV+ oropharyngeal → better prognosis
- Extracapsular spread and use of adjuvant chemo in HPV+ patients did not improve survival vs. RT alone
- HPV+ patients tend to be younger (age 40-60) with fewer comorbidities
- Reduce late toxicities, especially related to swallowing difficulties and need for enteral nutrition
- Methods: reduce or eliminate concurrent chemotherapy; reduce RT dose

Overall Survival

<table>
<thead>
<tr>
<th>Variable (multivariate)</th>
<th>HR</th>
<th>95% CI; p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV positive</td>
<td>0.33</td>
<td>0.2-0.5; p&lt;0.001</td>
</tr>
<tr>
<td>Drinking</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Older Age</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T4</td>
<td>2.08</td>
<td>1.6-3.5; p&lt;0.001</td>
</tr>
<tr>
<td>N2b-3</td>
<td>2.33</td>
<td>1.6-3.4; p&lt;0.001</td>
</tr>
<tr>
<td>RT alone</td>
<td>2.07</td>
<td>1.4-3.1; p&lt;0.001</td>
</tr>
<tr>
<td>&gt;10 pack-year smoker</td>
<td>1.72</td>
<td>1.1-2.7 (p=0.02)</td>
</tr>
</tbody>
</table>

Similar outcomes for relapse-free survival, except >10 year smoker – NS

RPA for Distant Metastases

<table>
<thead>
<tr>
<th>Low-Risk HPV+</th>
<th>High-Risk HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 1-3 and N0-2c</td>
<td>N3</td>
</tr>
<tr>
<td>N2b if &lt;10 pack-years</td>
<td>T4</td>
</tr>
<tr>
<td>Equally likely to get RT alone or CRT</td>
<td></td>
</tr>
<tr>
<td>Disease control same with RT and CRT by T but lower for RT alone if N2b or N2c</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-Risk HPV-</th>
<th>High-Risk HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 1-2 and N0-2C</td>
<td>T3-4 and N3</td>
</tr>
</tbody>
</table>

Ongoing Trials

- ECOG E1308 – induction cisplatin, cetuximab, paclitaxel → concurrent RT and cetuximab (RT dose based on response)
- RTOG 1016 – RT with concurrent cisplatin vs. RT with concurrent cetuximab
- Vaccines
  - MAGE-A3/HPV16 for recurrent, progressive, or metastatic oropharyngeal (U. Maryland)
  - REALISTIC (United Kingdom) – recombinant listeria HPV 16

HN

- HN is a 45 year-old male with stage III oropharyngeal cancer with no smoking or drinking history. He is otherwise in good health. Should HN receive concurrent chemotherapy along with his definitive radiation therapy regimen?
  - 1. yes
  - 2. no
Summary

- HPV+ (esp. type 16) oropharyngeal cancer patient have better prognosis and treatment response based on retrospective data
- Recursive partitioning analysis suggests a subset of HPV+ patient with low risk for distant metastases may be candidates for de-intensified therapy (reducing or eliminating chemotherapy)
- AJCC has recently updated staging to include HPV as a prognostic category
- NCCN has not yet (8/16/2015) updated guidelines based on HPV status