Treatment of High-Grade Anal Dysplasia

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Fundació Lluita contra la Sida
Context

- What is the problem?
- What are we doing about it?
- What do we need to do better?
KEEP CALM AND EVALUATE
HPV Associated Cancers

Gillison ML 2008 Cancer
Anal Cancer Incidence and HIV

Incidence rate (per 100,000 person-years)

Calendar era

Global P value = .078

Global P value = .655

96–99 00–03 04–07 96–99 00–03 04–07

90 (Ref)

159 (P = .33)

131 (P = .03)

28

45

57 (P = .7)
# Anal Cancer Survival

Stage distribution and 5-year relative survival by stage at diagnosis for 1999-2006, all races, both sexes

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage distribution (%)</th>
<th>5-year relative survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site)</td>
<td>50</td>
<td>80.1</td>
</tr>
<tr>
<td>Regional (spread to regional LN)</td>
<td>29</td>
<td>59.8</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>12</td>
<td>30.5</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>9</td>
<td>56.0</td>
</tr>
</tbody>
</table>

SEER database
As shown in this illustration, with increasing severity of SIL, of either the cervix or anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from one or more foci of high-grade SIL (HSIL), as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL.

**Source:** Joel Palefsky, MD, FRCP(C)
Anal Dysplasia as an Anal Cancer Precursor

- Comparing anal dysplasia/cancer with cervical dysplasia/cancer:
  - Same HPV risk types (16/18)
  - Similar cytology/pathology
  - Similar cytology sensitivity
  - Same chromosomal abnormalities
  - Frequently diagnosed simultaneously
  - Established progression of perianal Bowen’s disease
  - No randomized controlled trial

SUN Study

- Observational prospective cohort study looking at annual incidence of abnormal cytology after negative cytology in 700 HIV-infected participants in 4 US cities

- Incidence of abnormal anal cytology at follow up
  - MSM – 16.2 per 100 person years
  - Women – 11.1 per 100 person years
  - MSW – 9.9 per 100 person years

- Factors associated with incident abnormal anal cytology
  - MSM
  - Age > 36 years
  - Unprotected RAI
  - Detection of HPV genotypes at baseline (LR or HR)
Risk Factors for Progression from LSIL to HSIL

- HIV infection with CD4 count <200 cells/µL
- Infection with multiple HPV types
- Prevalent high-level of high-risk HPV DNA
- Abnormal anal cytology (HSIL>LSIL)
- Abnormal HRA examination
HSIL Regression, and HAART Effect

- Previously generally accepted that HSIL rarely regresses
  - Study from the SPANC group showed ~25% regression of HSIL (AIN 2/3)
- More recent studies indicating a protective effect of ART (or early ART) and a stable sexual relationship

Progression of HGAIN to Cancer

- 5/32 (16%) HIV-infected patients with HGAIN at a mean of 6 years of follow up
  - Condyloma Rx only
- 5/36 (14%) HIV-infected patients with perianal HGAIN after a mean of 2.2 years of follow-up
  - Imiquimod and some surgery
- 8/55 (15%) with AIN 2/3 developed cancer with a median follow-up of 5 years
  - No Rx
- 2/184 (1%) in UCSF cohort of extensive HGAIN developed anal cancer
  - Aggressive surgery and office based Rx
- 21 patients were identified with cancer from a previously-biopsied site of HGAIN at UCSF

ANCHOR Study

- Objective: To show that treatment of anal HSIL will reduce the risk of invasive anal cancer
- Randomized clinical trial enrolling 5000 HIV-infected adults age 35 or older with anal HSIL
- One arm receives best available treatment of anal HSIL vs. active monitoring without treatment
- Endpoint: Anal cancer
ANCHOR Study Design

Estimated < 50 develop cancer
Controversies in Anal Cancer Screening

- General acceptance that HSIL precedes anal cancer but most people with HSIL will never develop cancer
- Treatments for HSIL are not well studied but are clearly less effective than those for cervical intraepithelial neoplasia
- Assessment by HRA and treatment of HSIL can be difficult
- Few data on non-HIV infected immunosuppressed populations (solid organ transplant recipients, stem cell transplants)
- Not yet recommended by national organizations setting standards for health care maintenance
KEEP CALM AND START THE CONVERSATION
The Conversation

- Consider:
  - Side effects of treatment
  - Quality of life
  - Regression
  - Recurrence
  - Anal cancer (late) presentation
  - Anal cancer treatment morbidity
Surgery and Electrofulguration

- HRA directed surgical treatment
- 29 HIV-infected and 8 uninfected MSM
- Mean age 45+/- 8 yrs
- Follow up approx. 30 months
  - HIV uninfected: no recurrence
  - HIV-infected: 23/29 (79%) had recurrent or persistent HSIL
    - 6 were re-treated and 4 recurred
- No SAE

Chang Dis Colon Rectum 2002
80% Trichloroacetic Acid
80% Trichloroacetic Acid

- HIV-infected MSM
- TCA applied 5 x with Q-tip
  - 98 lesions in 72 patients
  - 77 (78.6%) resolved to LSIL or normal
  - 48 (49.0%) and 27 (27.6%) lesions resolved with 1 and 2 TCA treatments
  - 8 (15.1%) of 53 patients had a lesion that recurred at the index site
- No SAEs
Infrared Coagulation
Infrared Coagulation

- HIV-infected men and women
- 66 patients with HSIL treated (cytology ASCUS (14%), LSIL (27.5%), HSIL (8%))
- At 12 months
  - all patients had normal anal cytology
- At a mean of 30 months (18-43)
  - 7/66 (13%) had HSIL
Electrocautery

- 83 HIV-infected MSM
- Assessed at 6-8 weeks following procedure/s
  - Complete response: 27 (32%)
  - LSIL: 28 (34%)
  - Persistence 28 (34%)
- At a mean of 30 months, 14/55 (25%) had HSIL
- No SAE
5% Imiquimod
5% Imiquimod

- Double blind randomized placebo controlled study in HIV-infected participants
  - 64 enrolled and 53 completed (1 d/c due to S/E)
  - Self applied imiquimod (28)/placebo (25) 3 x per week x 4 months
  - Anal cytology, HRA and biopsy at 6 months
    - Imiquimod: 4 resolved, 8 LSIL (43%)
    - Placebo: 1 resolved (4%)
  - Open label: 5 cleared and 4 LSIL
  - Overall 63% response during follow up to 36 months
5-Fluorouracil
5% Fluorouracil

- 11 HIV-infected patients with internal anal dysplasia
  - 6 (55%) clinical improvement with reduction of volume
  - 3 (27%) improvement of dysplasia grade
  - 8 (73%) had mild/moderate perianal irritation requiring dose reduction in 6
Cidofovir
1% Cidofovir

- 24 HIV-infected men and 9 HIV-infected women with anal and vulvar HSIL ≥3 cm²
- Topical application for 6 2-week cycles
- 26 (79%) completed treatment
  - 5 (15%) complete response
  - 12 (36%) partial (over 50% reduction in size)
  - 7 (21%) stable
  - 2 (6%) progressed
- Burning/irritation in 25, ulceration in 13
Radiofrequency Ablation

- 21 HIV-uninfected participants
- HSIL less than 50% circumference
- HRA every 3 months for 12 months
  - 6 (29%) recurrence
  - 4 (19%) had persistence of index lesion at 3 months
- New procedure and impact of learning curve on lesion Rx efficacy
- No SAE
## Treatment of HSIL in HIV-infected MSM

<table>
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<tr>
<th>Treatment</th>
<th>Efficacy</th>
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<tr>
<td>Excision/Electrofulguration</td>
<td>20%</td>
</tr>
<tr>
<td>Infrared coagulation</td>
<td>65-70%</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>66%</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td>76%</td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>70%</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>60-70%</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>51%</td>
</tr>
<tr>
<td>Combination</td>
<td>70%</td>
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Recurrence by Study

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<td>Combination Rx in HIV-infected patients</td>
<td>1 year: 50% and 2 year: 70 %</td>
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References:
Summary of Treatments

- Ablative treatments are commonly used
  - Generally well tolerated
  - Disease recurrence is very common
  - Responses are suboptimal
- Topical treatments are alternatives
  - 5 fluorouracil, imiquimod, and application of TCA are used in practice.
- Prospective studies are lacking, better treatments are needed
KEEP CALM AND DO NO HARM
Summary

- Partner with patients to understand their treatment needs
- Discuss the range of treatment modalities
- Prioritize minimally invasive treatment
- Plan for recurrence and re-treatment
- Educate on symptoms suggestive of progression
Future

- Prophylactic vaccination
- Therapeutic vaccination
- Increase anal cancer awareness in at-risk populations
- Rationalize treatment based on biomarkers
- Normalize DARE as a routine aspect of physical examination in at-risk populations
Thank You