Malignancy in Myanmar with focus on cervical cancer

Ed Wilkins
Aim for today

• What are the types of cancer seen in HIV?
• What characteristics do ADM share/not share?
• Which ADM and NADM are common in Myanmar?
• Distinguishing HIV related cancers from OI’s
• What is the relationship between HIV and cervical cancer?
• What characteristics do cervical cancer share/not share?
What are the types of cancers seen in HIV?
ADM and NADM

- AIDS-defining malignancies (ADM)
- Kaposi’s sarcoma
- Non-Hodgkin lymphoma
- Primary CNS lymphoma
- Cervical cancer
ADM and NADM

Non-AIDS defining malignancies (NADM)

- Anal cancer
- Hodgkin disease
- Hepatoma
- Lung cancer
- Testicular cancer
- SCC conjunctiva, mucous membranes
- Many other sites..
What characteristics do ADM and NADM share?
Both are more common in HIV than in non-HIV

Standardised rate ratio of ADM and non-ADM in HIV-infected population: general population, 1992–2003*

*Calculated as ratio of incidence in ASD/HOPS population : standardised incidence in SEER population
Both are associated with increasing rates with lower CD4 counts

### Mortality rates by CD4 count in individuals with ADM and non-ADM

<table>
<thead>
<tr>
<th>Latest CD4 count (/µL)</th>
<th>Person-years (py)</th>
<th>Non-ADM</th>
<th>ADM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (/1000py) (n)</td>
<td>Relative risk*</td>
<td>Rate (/1000py) (n)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>2335</td>
<td>6.0 (14)</td>
<td>15 (&lt;0.001)</td>
</tr>
<tr>
<td>50–99</td>
<td>2295</td>
<td>9.6 (22)</td>
<td>19 (&lt;0.001)</td>
</tr>
<tr>
<td>100–199</td>
<td>8097</td>
<td>6.8 (55)</td>
<td>10 (&lt;0.001)</td>
</tr>
<tr>
<td>200–349</td>
<td>21,048</td>
<td>2.0 (43)</td>
<td>3 (&lt;0.001)</td>
</tr>
<tr>
<td>350–499</td>
<td>24,052</td>
<td>1.1 (27)</td>
<td>2 (0.03)</td>
</tr>
<tr>
<td>500+</td>
<td>46,903</td>
<td>0.6 (27)</td>
<td>1 (–)</td>
</tr>
</tbody>
</table>

*Adjusted for cohort, age, gender, smoking status, weight, transmission group, ethnicity, prior non-fatal non-neoplastic AIDS, HCV and HBV status, cART exposure, and latest HIV-RNA level

Both are associated with oncogenic viruses

<table>
<thead>
<tr>
<th>AIDS-Defining</th>
<th>Oncogenic virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Kaposi’s Sarcoma</td>
<td>HHV-8</td>
</tr>
<tr>
<td>• Non-Hodgkin’s Lymphoma</td>
<td>EBV, HHV-8</td>
</tr>
<tr>
<td>• PCNSL</td>
<td>EBV</td>
</tr>
<tr>
<td>• Invasive Cervical Carcinoma</td>
<td>HPV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-AIDS Defining (e.g.)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anogenital cancers</td>
<td>HPV</td>
</tr>
<tr>
<td>• Hodgkin’s Disease</td>
<td>EBV</td>
</tr>
<tr>
<td>• Leiomyosarcoma (pediatric)</td>
<td>EBV</td>
</tr>
<tr>
<td>• Squamous Conjunctival Carcinoma</td>
<td>HPV</td>
</tr>
<tr>
<td>oesophagus, larynx, lip</td>
<td></td>
</tr>
<tr>
<td>• Hepatoma</td>
<td>HBV, HCV</td>
</tr>
</tbody>
</table>
What characteristics do ADM and NADM not share?
For ADM the absolute risk is greater and varies more by type and CD4 count

Standardised incidence ratio of ADM by CD4 count, from AIDS and cancer registries USA, 1990–1996

CD4 count cells/mL
- Orange: >200
- Yellow: 100–199
- Purple: 50–99
- Red: <50

ADM incidence has fallen sharply with use of ART

- ART protects against development
- Independent of type of ART

Buchacz K et al. AIDS 2010, 24:1549–1559
NADM incidence has increased as ADM has decreased (USA 1991-2005)

HIV-AIDS cancer match study USA

AIDS-defining malignancy

Non-AIDS-defining malignancy

Shiels et al. 2010
Factors Contributing to the Increase in NADM cases in HIV

- 4-fold increase in HIV/AIDS Population
- Patients living longer and not dying of OI
- Rising proportion of HIV pts > 50 yo
- Cancer incidence increases with age
- Greater and earlier start to smoking in HIV
- Increase in some CA incidence rate among HIV
  - Lung (3X), anal (29X), liver (3X), HL (13X)
  - Suggests may be additional risk from HIV
Crude Incidence Rates of Cancer Among 20,775 HIV-Positive Patients Enrolled in Kaiser Permanente California (1996-2008), by ART Use Status

ART reduced the incidence of ADM but not NADM
Which ADM are common in Myanmar?
Myanmar: age standard incidence cancer and mortality rates

Men

Women

Non-Hodgkin lymphoma

Breast

Cervix uteri
Kaposi’s sarcoma: Myanmar
Age specific rate 0.03/10^5

Source: GLOBOCAN 2012 (IARC)
KS by region: incidence and mortality
Non-Hodgkin’s Lymphoma: Myanmar
Age specific rate 3.54/10^5
NHL by region: incidence and mortality
Current and predicted increase of KS and NHL
Cervical cancer: Myanmar
Age specific rate 20.57/10^5

Source: GLOBOCAN 2012 (IARC)
Cervical cancer: incidence and mortality
Current and predicted increase of cervical cancer

International Agency for Research on Cancer

Myanmar
Cervix uteri
Number of new cancers in 2020 (all ages)

- Incidence in 2012
- Demographic effect

GLOBOCAN 2012 (IARC) (24.4.2016)
Which NADM are common in Myanmar?
Myanmar: age standard incidence cancer and mortality rates
Lung cancer: Myanmar
Age specific rate 20.2/10^5
Liver cancer: Myanmar
Age specific rate 6.41/10^5
Distinguishing HIV-related cancers from OI’s

Lymphoma
Patient

- 37y-old ex-IDU for 8y
- Travelled Asia/Europe ++
- Presented with 6w history of fever, sweats, loss of weight
- HIV +ve, CD4 280 cells/mm³, VL 295,000 c/ml
- On methadone
Time course of symptoms

- Fevers/sweats
- Loss of weight
- Neck nodes

Weeks
Differential diagnosis – peripheral and mediastinal lymphadenopathy

HIV disease and malignancies

- Progressive generalised lymphadenopathy
- Non-Hodgkin’s lymphoma
- Hodgkin’s lymphoma
- Multicentric Castleman’s disease

Opportunistic infections

- TB
- MAI
- Penicilliosis
- Histoplasmosis
- Cryptococcus
HIV disease and malignancies

- Progressive generalised lymphadenopathy
- Non-Hodgkin’s lymphoma (BL)
- Hodgkin’s lymphoma
- Multicentric Castleman’s disease

Opportunistic infections

- TB
- MAI
- Penicilliosis
- Histoplasmosis
- Cryptococcus
Biopsy result revealed Hodgkin’s disease

- Biopsy - Reed-Sternberg cell
- CT:
  - Mediastinal mass, splenomegaly
- Bone marrow clear
- CSF cytology clear
- Type B symptoms: fever, loss of weight or night sweats
- **Stage 3b**
Lymphoma is more than one condition and not all are classical ADM

<table>
<thead>
<tr>
<th>Disease</th>
<th>Median CD4 range at diagnosis</th>
<th>Infective factor/co-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL: Burkitt’s</td>
<td>350–500</td>
<td>EBV</td>
</tr>
<tr>
<td>NHL: Diffuse large B-cell</td>
<td>10–150</td>
<td>EBV</td>
</tr>
<tr>
<td>NHL: PCNSL</td>
<td>10–50</td>
<td>EBV</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>100–200</td>
<td>HHV-8</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>100–500</td>
<td>EBV</td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>100-300</td>
<td>HHV-8</td>
</tr>
</tbody>
</table>

Personal communication on file. Dr Edmund Willkins, 2008.
Few facts about Hodgkin’s disease

• It is a non-AIDS defining malignancy (NADM)
• 10-20x commoner in HIV
• 90% have ‘B’ symptoms
• 74–92% have advanced stages of disease
• Frequent involvement of extra-nod al sites:
  • Bone marrow (40–50%); Liver (15–40%) and spleen (20%)
• HIV-HL tends to develop as an earlier manifestation of HIV
• Higher CD4 and often ART suppressed
Few facts about non-Hodgkin’s lymphoma

- Second most common malignancy in HIV
- AIDS defining (ADM) but Burkitt’s lymphoma occurs at higher CD4 count
- Several pathological types
- Prognosis improved with additional HAART and approaching that seen in HIV-negative persons
- Frequent extranodal sites involved
- HIV-related primary effusion lymphoma (PEL) is linked to HHV8 and is rare
  - Very poor prognosis
Presentation usually associated with lymphadenopathy

- Majority of patients present with:
  - Type B symptoms – fevers, sweats and weight loss
  - Lymphadenopathy which may be generalised or localised
Half have visceral/extra-nodal disease

- Extra-nodal disease is common
- Sites of extra-nodal involvement include:
  - Oral cavity
  - Liver, spleen
  - GI tract (ileum)
  - Lung
  - Skin
  - Bone-marrow
Lymphoma Treatment

HAART
Cervical cancer in HIV
What is the relationship between HIV and cervical cancer?
HPV/HIV link

- HIV
- CIN/Ca cervix
- HPV
Cervical Cancer

• Latest data on cervical cancer incidence and mortality (GLOBOCAN 2012, IARC*):
  • 4\textsuperscript{th} most common cancer in women
  • Globally 528,000 cases diagnosed in 2012:
    • 86\% of all cases (n=453,032) in developing world
  • Globally 274,967 deaths:
    • 88\% of all deaths (n=241,818) in developing world
• Mortality to incidence ratio:
  • Developed countries: 36–43\%
  • Developing countries: 54–80\%

*www.iarc.fr/globocan2008
Association between HIV, CIN, and Cervical Cancer

• In HIV-positive women, there is a higher incidence of:
  • HPV infection (70-80% vs. 30%)
  • Persistent HPV with multiple and high-risk types (16/18)
  • Cervical cancer precursors (CIN)
  • Cervical cancer
• ART has minimal effect on CIN progression
Association between HPV and HIV

- Addition of HPV genotypes
- Transition between CIN III and cancer

What characteristics does cervical cancer share with other ADM?
It is more common in HIV-infected persons

Standardised incidence ratio of ADM by CD4 count, from AIDS and cancer registries USA, 1990–1996

CD4 count cells/mL

- >200
- 100–199
- 50–99
- <50

Significant association between CIN and HIV and with low CD4

1. HIV Immunosuppression
   a. HIV+
   b. HIV+, CD4 <200
   HIV+, CD4 200-499
   HIV+, CD4 ≥500

2. Non-HIV Immunosuppression
   a. Immunosuppressive therapy
   b. Solid organ transplant
What characteristics do cervical cancer and other ADM not share?
Relative risk and relationship to CD4 is much less than with other ADM’s

Standardised incidence ratio of ADM by CD4 count, from AIDS and cancer registries USA, 1990–1996

CD4 count cells/mL
- >200
- 100–199
- 50–99
- <50

There has been little change in incidence and no impact from ART.

SIR vs. HIV-ve women 5.6 for invasive cancer

HPV vaccines are available and highly effective
Potential to eradicate all HPV-related disease

Relative reduction of genital warts aged 16-28 with vaccination programme
Reduction in most oncogenic strains

Differences in HPV Genoprevalence Between Pre-vaccine and Post-vaccine Female Populations in Australia

- Any HPV: Pre-vaccine 59.9%, Post-vaccine 48%, P=0.006
- HR-HPV: Pre-vaccine 47%, Post-vaccine 34.2%, P<0.05
- HR-HPV, excluding 16, 18: Pre-vaccine 37.6%, Post-vaccine 31.2%, P=0.10
- HPV 6, 11, 16, 18: 75% fall from 28.7% to 6.7%, P<0.001
CIN III reduction in young women
Lastly, a screening programme exists which is highly effective

- Increased rate of Cervical Ca can be avoided with regular screening programmes
  - Rates before and after screening reduced 5-10 fold
  - 75% of cases of cancer can be prevented
  - Increased rate associated with HIV can be abolished with screening
- All HIV-infected women should have annual cytology
  - Same age range as for HIV-negative women (1B)
But..

Screening programs remain difficult to implement in low and middle-income settings.
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Discussion and questions?
Malignancy in Myanmar with focus on cervical cancer