Treating cancer in HIV infected patients

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National Centre for HIV malignancy
Chelsea & Westminster Hospital
## AIDS defining malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>KSHV</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (including primary cerebral lymphoma)</td>
<td>EBV</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>HPV</td>
</tr>
</tbody>
</table>

Rate ratio (RR) for 1997-9 versus 1992-6

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Virus</th>
<th>RR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>KSHV</td>
<td>0.32 (0.03)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (including primary cerebral lymphoma)</td>
<td>EBV</td>
<td>0.58 (0.06)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>HPV</td>
<td>1.87 (0.65)</td>
</tr>
</tbody>
</table>
AIDS defining malignancies declining incidence

Adapted from Shiels MS et al. J Natl Cancer Inst 2011;103:753-62
### START trial: An Oncologist’s view

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Immediate initiation group (n=2326)</th>
<th>Deferred initiation group (n=2359)</th>
<th>Hazard ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>/100 PY</td>
<td>N</td>
<td>/100 PY</td>
</tr>
<tr>
<td>KS</td>
<td>1</td>
<td>0.01</td>
<td>11</td>
<td>0.16</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3</td>
<td>0.04</td>
<td>10</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Non-AIDS Defining Malignancy (NADM) not declining

Incidence rate per 100,000 PY

Age (years)
- 60 and older
- 50–59
- 40–49
- 30–39
- 20–29
- 13–19
- 0–12

Adapted from Shiels MS et al. J Natl Cancer Inst 2011;103(9):753–62
D:A:D More deaths due to NADM

Cause of death 1999-2000
- NADM: 8%
- Other causes: 92%

Cause of death 2009-2011
- NADM: 20%
- Other causes: 80%

Worm SW, BMC Infect Dis. 2013; 13: 471
Age distributions: HIV/AIDS & general populations

More cancers
Different cancers
Cancer: UK Age-Specific Incidence Rates 2010

Data from CRUK
## Most common cancers by age

<table>
<thead>
<tr>
<th></th>
<th>25-49 years</th>
<th>50-74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>Testis cancer</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>Breast cancer</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Cervical cancer</td>
<td>Colorectal cancer</td>
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</tbody>
</table>
Treatment of NADM: Things to worry about....

Effects of chemo on CD4 & VL

Pharmacokinetic interactions (cART & chemo)
Effects of chemotherapy on CD4 & VL

On average CD4 falls by 50% but no change in plasma HIV viral load.
OI prophylaxis

Routine OI prophylaxis
Co-trimoxazole
Fluconazole
Azithromycin
Aciclovir
Drug interactions?

Antiretrovirals

Chemotherapy
Strong inhibitors of CYP3A4

>80% decrease in clearance or >5 fold rise in AUC

Protease inhibitors (ritonavir, cobicistat)
Macrolide antibiotics (clarithromycin)
Azole antifungals (ketoconazole, itraconazole)
CYP3A4 cytotoxic substrates

- Anthracyclines (*-rubicin)
- Vinca alkaloids (vinc-*)
- Topoisomerase inhibitors (etoposide & irinotecan)
- Taxanes (*-taxel)
- Sorafenib, sunitinib, vemurafenib, gefitinib, erlotinib, imatinib.......(*-nib)
Outcomes are similar in HIV+ and HIV- people if the treatment is the same

As long as:
(i) the HIV is diagnosed and treated too
(ii) Opportunist infection prophylaxis is given
(iii) Pharmacokinetic interactions are considered
Hodgkin’s Disease overall survival: no influence of HIV status
Overall survival Anal Cancer: no influence of HIV status

N = 75

<table>
<thead>
<tr>
<th>5 year survival</th>
<th>HIV+ (CWH)</th>
<th>CRUK</th>
</tr>
</thead>
<tbody>
<tr>
<td>65% (59-71%)</td>
<td>60% (male)</td>
<td></td>
</tr>
</tbody>
</table>
Testicular cancer survival: no influence of HIV status

- HIV+ n=35
- HIV- n=105

Chi-Square 0.075
DF 1.0
p=0.7838
Immune checkpoint inhibition
Adaptive cellular immune response to cancer

Antigen priming of T-cells

Effector phase
Antigen priming of T-cells

1. Dendritic cells present antigens via the major histocompatibility complex (MHC) to T-cell receptor (TCR)

2. A second signal is delivered by B7: Bind CD28 activates T-cell
Bind CTLA-4 inhibits T-cell

CTLA-4 = Cytotoxic T-lymphocyte-associated antigen
**Effector phase (killing cancer cells)**

- Primed T-cell recognizes the cancer antigen and kills the tumour cell.

- This is stopped if PD-1 (on T-cell) binds PD-L1 on cancer cell.
Checks and balance at the Immunological Synapse (negative feedback loops)

Nivolumab
Pembrolizumab
Inhibits effector phase

Ipilimumab
Blocks antigen priming
Immune checkpoint inhibitors (ICIs)

**Indications**
- NSCLC
- Metastatic Melanoma
- Renal Cell Carcinoma
- Metastatic Bladder Cancer
- Hodgkin Lymphoma

**Side Effect Profile**
- Immune-mediated adverse events; -itis events
- Diarrhea, cough, skin irritation, hepatitis, endocrinopathies, fatigue
- Manage with steroids and holding medication until resolution
What about ICIs in PLWH?

1. Is the target (PD-L1) expressed by the cancer cells in PLWH?

2. Are ICIs effective in PLWH?

3. What is the effect of ICIs on HIV?
Target expression in NSCLC: No influence of HIV status

24 HIV-associated NSCLC: 45% express PD-L1 and 33% express PD-L2
Same as matched HIV-ve NSCLC controls

Ann Oncol. 2018;29(6):1486-1488
Do immune-checkpoints contribute to KS resistance to cART?

10 HIV+ MSM with progressive KS despite cART and plasma HIV VL<20 copies/mL
Immune-checkpoints contribute to KS resistance to cART

50% had KS spindle cells expressing PD-L1

KS expressing PD-L1 had denser tumour infiltrating CD8 lymphocytes

Oncoimmunology. 2017;6(8):e1304337
Nivolumab in HIV+ KS

8 HIV+ Patients
75% had CD4 count >200 and undetectable HIV viral load
Median follow up 3.5 months
Response rate 63% (5/8)
No rebound in viral load
Rise in CD4 (+80)

Journal of Clinical Oncology 36, no. 5_suppl (February 2018) 63
What about the effects on HIV?
2009

Increased expression of PD-1 and PD-L1 on CD4 & CD8 cells in PLWH

Blocking PD-1 or PDL-1 with mouse mAbs increased anti-HIV gag specific responses
Nivolumab in HIV+ NSCLC

Nivolumab (anti-PD-1) for relapsed lung cancer (single patient).
During treatment:
1. plasma HIV RNA level increased from <20 copies/mL to 101 copies/mL (viral blip)
2. expansion of HIV-specific CD8 cells
3. HIV DNA level fell from 369 to 30 copies/million cells

Decline in total HIV DNA on Nivolumab

- HIV-DNA (copies/10^6 cells)
- HIV-RNA (copies/ml)
- CD4/mm^3
- CD8/mm^3
- IL-6*10 (pg/ml)

Plasma HIV RNA blip

Nivolumab
But...previously no effects

Ipilimumab (anti-CTLA-4)
Transient rise in HIV RNA but no effect on HIV reservoirs

Nivolumab (anti PD-1)
Increase in HIV-specific T cells but no effect on HIV reservoirs
CWH patients on Nivolumab (3months)

Before
After
100
1000
10000
Copy/ 10^6 CD4
Total HIV DNA

Before
After
100
1000
10000
Copy/ 10^6 PBMCT
Total HIV DNA

Centre for Immunology and Vaccinology

Imperial College London
CWH patients on Nivolumab (3months)

Integrated HIV DNA

- MH1
- NET
- NSCLC

Integrated HIV DNA

- MH1
- NET
- NSCLC

Before
After

Copy/10^6 PBMC

Copy/10^6 CD4

Centre for Immunology and Vaccinology
Treating cancer in HIV infected patients: summary

• Outcomes are similar in PLWHIV and HIV- people if the treatment is the same
• As long as the HIV is diagnosed and treated too
• Attention to drug interactions and OI prophylaxis