HIV and Chemotherapy: What Do We Really Need to Know?
Morgan Pendleton, PharmD
mpendlet@wakehealth.edu

Wake Forest Baptist Medical Center

Objectives
• Summarize AIDS-related malignancies
• Review drug metabolism of relevant HIV and oncology medications
• Understand medication concerns in oncology patients with HIV
• Evaluate and apply current literature to clinical practice

Background
• > 1 million people in the United States are living with HIV
  • 500,000 are living with AIDS
• Approximately 50,000 people become infected each year in the United States
• AIDS diagnosis
  • HIV-positive
  • AIDS-defining illness
  • CD4 count < 200 cells/mm³

Lancet 2007;370(9581):59-67
Wake Forest Baptist Medical Center

AIDS-Defining Infections
• Multiple or recurrent bacterial infections
• Candidiasis
• Coccidioidomycosis
• Cryptosporidiosis
• Cytomegalovirus infection
• Herpes simplex infection
• Histoplasmosis
• Isosporiasis
• Mycobacterium infection
• Pneumocystis jirovecii infection
• Recurrent pneumonia
• Salmonella septicaemia
• Toxoplasmosis

Wake Forest Baptist Medical Center

AIDS-Defining Syndromes
• HIV-related encephalopathy
• Lymphoid interstitial pneumonia
• Progressive multifocal leukoencephalopathy
• Wasting syndrome attributed to HIV

Wake Forest Baptist Medical Center

Wake Forest Baptist Medical Center
AIDS-Defining Malignancies

- People infected with HIV/AIDS have a higher risk of developing certain cancers due to a weakened immune system and inability to fight infection.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Associated Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human herpes virus 8 (HHV-8)</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Epstein Barr virus (EBV)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>Cervical, anal, penile, vaginal, vulvar, and</td>
</tr>
<tr>
<td></td>
<td>head and neck cancers</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Liver cancer</td>
</tr>
</tbody>
</table>

- Increased incidence in HIV population

- Risk Based on HIV Status

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Fold Increase Compared to HIV-Negative People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>Several thousand</td>
</tr>
<tr>
<td>non-Hodgkin’s lymphoma</td>
<td>70</td>
</tr>
<tr>
<td>Cervical</td>
<td>9</td>
</tr>
</tbody>
</table>

Lancet 2007;370(9581):59-67
Lancet 2007;370(9581):59-67

Drug Metabolism of Relevant HIV and Oncology Medications

- Drug Metabolism

- Cytochrome P450 Metabolism

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors</th>
<th>Strong CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Modafinil</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>

Most potent CYP3A4 inhibitor

*These lists are not all inclusive.*
Cytochrome P450 Metabolism

<table>
<thead>
<tr>
<th>Major Substrates of CYP3A4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Tacrolimus</td>
</tr>
</tbody>
</table>

This list is not all inclusive.

**Patient Cases**

**Case**
- 38 year old AAM
- **HPI**
  - Severe mouth pain due to grade 3-4 mucositis
  - Intolerable of liquids
- **PMH**
  - HIV
  - Chronic kidney disease
  - Left hard palate squamous cell carcinoma (SCC)

**Case**
- Darunavir 600 mg BID
- Etravirine 200 mg BID
- Ritonavir 100 mg BID
- Zidovudine 300 mg BID
- Chemoradiation with Docetaxel 20 mg/m² (dose reduction/multiple delays due to toxicity)
- **MISC**
  - Fentanyl 50 mcg/hr patch
  - Dapsone 100 mg daily
  - Azithromycin 1200 mg once weekly

**Case**
- 42 year old AAM
- **HPI**
  - New diagnosis of Kaposi’s Sarcoma
- **PMH**
  - HIV
  - Herpes zoster infection

**Case**
- Stridil 1 tablet once daily
- Etravirine 200 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg
- **KS**
  - Plan to initiate Paclitaxel 135 mg/m² every 3 weeks
- **MISC**
  - Sulfamethoxazole-Trimethoprim 800-160 mg MWF only
  - Valacyclovir 1000 mg TID
**Audience Response Question**

Which chemotherapy agent would be safe to administer with ritonavir?

- A. Vincristine
- B. Vinblastine
- C. Bortezomib
- D. Mitomycin

**Vinblastine/Vincristine**

- Toxicity assessment in 32 patients with HIV and Hodgkin's Disease/lymphoma
- Chemotherapy regimens included ABVD or MOPP
- HIV regimens including a PI: 19 (83%)
- HIV regimens not including a PI: 4 (17%)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Receiving HAART n = 23 n (%)</th>
<th>Not Receiving HAART n = 9 n (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity Overall</td>
<td>13 (57)</td>
<td>5 (22)</td>
<td>0.044</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1 (11)</td>
<td>1 (11)</td>
<td>-</td>
</tr>
<tr>
<td>Hematologic Toxicity Overall</td>
<td>17 (74)</td>
<td>3 (33)</td>
<td>0.049</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>14 (61)</td>
<td>3 (33)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Docetaxel**

- Mice model pharmacokinetic study assessing impact of CYP3A4 inhibitors and inducers
- Administered docetaxel with and without dexamethasone, efavirenz, ketoconazole, or ritonavir

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Half Life (hours)</th>
<th>AUC (µg l/h/ml)</th>
<th>AUC Fold Increase</th>
<th>Cmax (µg/mL)</th>
<th>Clearance (L/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel alone</td>
<td>6.4</td>
<td>10.3</td>
<td>-</td>
<td>18.1 ± 2.2</td>
<td>1.93</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>4.9</td>
<td>7.6</td>
<td>0.7</td>
<td>17.2 ± 3.9</td>
<td>2.59</td>
</tr>
<tr>
<td>Plus efavirenz</td>
<td>4.7</td>
<td>12.4</td>
<td>1.2</td>
<td>25.5 ± 3.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**Bortezomib**

- Prospective, multicenter, open-label, randomized, cross-over study
- 21 patients with advanced solid tumors
- Bortezomib was given 1 mg/m² IV (days 1, 4, 8, 11 of two 21-day cycles)
- Randomized to ketoconazole 400 mg on days 6, 7, 8, 9 of cycle 1 or 2

<table>
<thead>
<tr>
<th>Cycle</th>
<th>AUC (mg/ml/h)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Bortezomib alone</td>
<td>108 (25)</td>
</tr>
<tr>
<td></td>
<td>Bortezomib + ketoconazole</td>
<td>137 (69)</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>Bortezomib alone</td>
<td>171 (87)</td>
</tr>
<tr>
<td></td>
<td>Bortezomib + ketoconazole</td>
<td>244 (83)</td>
</tr>
</tbody>
</table>
### Bortezomib

<table>
<thead>
<tr>
<th>Hematologic Toxicity</th>
<th>Bortezomib Alone Mean (SD)</th>
<th>Bortezomib + Ketoconazole Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Neutrophil Count (x 10^9/L) Prior to Initiation</td>
<td>6.2 (3.8)</td>
<td>5.7 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Day 11</td>
<td>6.2 (5.0)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL) Prior to Initiation</td>
<td>12 (1.20)</td>
<td>11.9 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Day 11</td>
<td>11.7 (0.9)</td>
</tr>
<tr>
<td>Platelets (x10^9/L) Prior to Initiation</td>
<td>291 (133)</td>
<td>311 (163)</td>
</tr>
<tr>
<td></td>
<td>Day 11</td>
<td>212 (116)</td>
</tr>
<tr>
<td>White Blood Cell Count (x10^9/L) Prior to Initiation</td>
<td>8.3 (4.1)</td>
<td>7.7 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Day 11</td>
<td>8.2 (5.4)</td>
</tr>
</tbody>
</table>

### Irinotecan

- Prospective, open-label, randomized pharmacokinetic study
- Assessed irinotecan (CPT11) concentrations with and without lopinavir/ritonavir (LPV/RTV)
- 8 patients with Kaposi’s sarcoma and HIV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Irinotecan Alone (mean ± SD)</th>
<th>Irinotecan + LPV/RTV (mean ± SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>1,329 ± 310</td>
<td>1,594 ± 434</td>
<td>0.02</td>
</tr>
<tr>
<td>AUC (ug·A·h)</td>
<td>7,702 ± 2,205</td>
<td>14,334 ± 4,530</td>
<td>0.001</td>
</tr>
<tr>
<td>Clearance (L/h/m^2)</td>
<td>21.3 ± 5.3</td>
<td>11.3 ± 3.5</td>
<td>0.0008</td>
</tr>
<tr>
<td>Volume of Distribution at steady state (L/h/m^2)</td>
<td>188 ± 54</td>
<td>131 ± 37</td>
<td>0.007</td>
</tr>
</tbody>
</table>

### Tacrolimus

- Patient case involving sustained blood levels of tacrolimus after concurrent administration with ritonavir

### Application to Clinical Practice
Extrapolation of Antiretroviral and Chemotherapy Interactions

- **Taxanes**
  - Paclitaxel
    - Also metabolized by CYP2C8
    - Potentially less significant interaction
    - Severe neuropathy and hematologic toxicity

- **Vinca Alkaloids**
  - Vincristine
    - More potent microtubule inhibitor
    - Potentially more significant interaction
    - Severe neuropathy and bowel obstruction/perforation

Extrapolation of Antiretroviral and Chemotherapy Interactions

- **Stribild**
  - Cobicistat is also a potent CYP3A4 inhibitor
  - Increase chemotherapy exposure
  - Ketoconazole
    - Potent CYP 3A4 inhibitor
    - Azole antifungal use in the oncology population

---

**Audience Response Question**

What should you assess to determine if a theoretical interaction exists between a chemotherapy agent and an HIV medication?

A. Metabolism of both agents, including cytochrome P450 substrates, inhibitors, and inducers

B. Metabolism of both agents, including cytochrome P450 inhibitors and inducers

C. Metabolism of the chemotherapy agent alone

D. Metabolism of the HIV medication alone

---

**Summary**

- A significant drug interaction exists between potent CYP3A4 inhibitors and certain chemotherapy agents
  - Electronic medical record
  - Outpatient setting
  - Transition to antiretroviral therapy that does not involve a protease inhibitor or cobicistat
    - Truvada + Raltegravir was chosen for both patient cases

- Chemotherapy dose adjustments as last line option (minimal data to support)
  - Docetaxel: 50% dose reduction
  - Paclitaxel: consider dose reduction
  - Vincristine: recommend holding ritonavir
  - Vinblastine: consider dose reduction
  - Ritonavir kinetics
    - 3-5 hour half-life elimination
    - Can initiate chemotherapy approximately 24 hours after ritonavir administration and discontinuation

---

**HIV and Chemotherapy: What Do We Really Need to Know?**

Morgan Pendleton, PharmD
mpendlet@wakehealth.edu
References

• Abramowicz MD. "Inhibitors and Inducers of CYP Enzymes and P-Glycoprotein." The Medical Letter 2013;55(1417):1-4