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

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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/mm^3

Lancet 2007;370(9581):59-67

Background

- AIDS-defining illnesses
  - Confirms the diagnosis of AIDS
  - Serious and life-threatening diseases that occur in HIV-positive people
    - Infections
    - Syndromes
    - Malignancies

Lancet 2007;370(9581):59-67

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 septicemia
- Toxoplasmosis

Morbidity and Mortality Weekly Report, December 5, 2008 57;10:1-12

AIDS-Defining Syndromes

- HIV-related encephalopathy
- Lymphoid interstitial pneumonia
- Progressive multifocal leukoencephalopathy
- Wasting syndrome attributed to HIV

Morbidity and Mortality Weekly Report, December 5, 2008 57;10:1-12

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

Virus	Associated Malignancy
Human herpes virus 8 (HHV-8)	Kaposi's sarcoma
Epstein Barr virus (EBV)	Lymphoma
Human papillomavirus (HPV)	Cervical, anal, penile, vaginal, vulvar, and head and neck cancers
Hepatitis B virus (HBV)	Liver cancer
Hepatitis C virus (HCV)	Liver cancer

Morbidity and Mortality Weekly Report, December 5, 2008 57;10:1-12
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Risk Based on HIV Status

- AIDS-defining malignancies

Malignancy	Fold Increase Compared to HIV-Negative People
Kaposi's sarcoma	Several thousand
non-Hodgkin's lymphoma	70
Cervical	5

- Increased incidence in HIV population

Malignancy	Fold Increase Compared to HIV-Negative People
Anal	25
Liver	5
Lung	3
Hodgkin's disease	10
Head and Neck	Not Reported

Lancet 2007;370(9581):59-67
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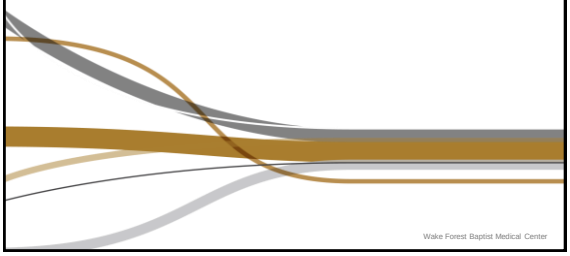
Drug Metabolism of Relevant HIV and Oncology Medications



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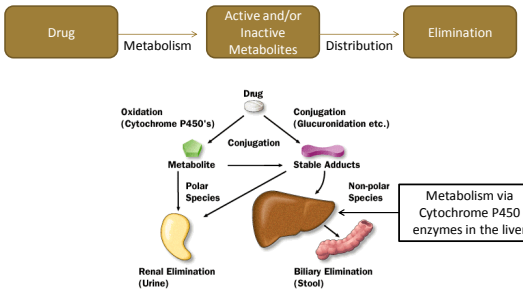
Drug Metabolism



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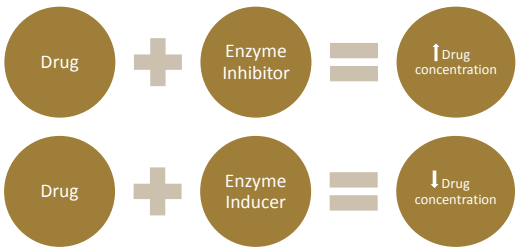
Cytochrome P450 Metabolism



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Cytochrome P450 Metabolism

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers
Atazanavir	Barbiturates
Clarithromycin	Carbamazepine
Cobicistat	Dexamethasone
Imatinib	Efavirenz
Isoniazid	Modafinil
Itraconazole	Nafcillin
Ketoconazole	Oxcarbazepine
Nelfinavir	Phenytoin
Posaconazole	Rifampin
Ritonavir ← Most potent CYP3A4 inhibitor	St. John's Wort
Voriconazole	

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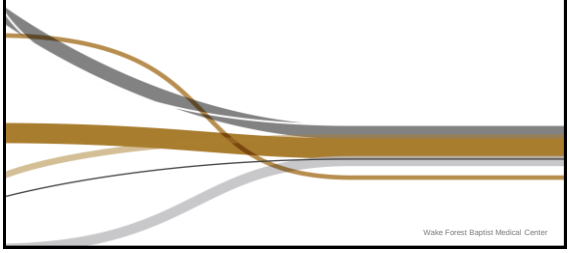
*These lists are not all inclusive

Cytochrome P450 Metabolism

Major Substrates of CYP3A4	
Docetaxel	Etoposide
Paclitaxel	Irinotecan
Vinblastine	Imatinib
Vincristine	Dasatinib
Vinorelbine	Nilotinib
Bortezomib	Erlotinib
Doxorubicin	Tacrolimus

*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

HIV
- Darunavir 600 mg BID
- Etravirine 200 mg BID
- Ritonavir 100 mg BID
- Zidovudine 300 mg BID

SCC
- Chemoradiation with Docetaxel 20 mg/m^2 (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

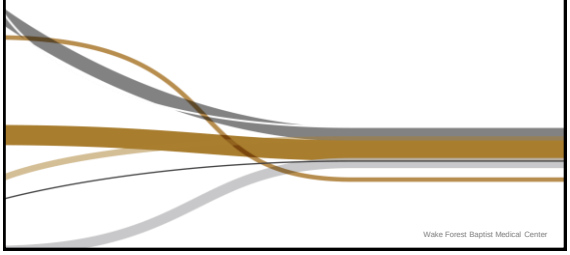
Case

HIV
- Stribild 1 tablet once daily
  - Elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir disproxil fumarate 300 mg

KS
- Plan to initiate Paclitaxel 135 mg/m^2 every 3 weeks

MISC
- Sulfamethoxazole-Trimethoprim 800-160 mg MWF only
- Valacyclovir 1000 mg TID

Literature Review



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%)

Toxicity		Receiving HAART n = 23 n (%)	Not Receiving HAART n = 9 n (%)	P-Value
Neurotoxicity	Overall	13 (57)	5 (22)	0.044
	Grade 3-4	1 (11)	1 (11)	-
Hematologic Toxicity	Overall	17 (74)	3 (33)	0.049
	Grade 3-4	14 (61)	3 (33)	-

Leukemia and Lymphoma December 2012;53(12):2390-2396

Docetaxel

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

Inducers	Half Life (hours)	AUC (µg/ h/ml)	AUC Fold Increase	Cmax (µg/mL)	Clearance (L/h/kg)
Docetaxel alone	6.4	**10.3**	-	18.1 ± 2.2	1.93
Plus dexamethasone	4.9	**7.6**	**0.7**	17.2 ± 3.9	2.59
Plus efavirenz	4.7	**12.4**	**1.2**	25.5 ± 3.2	1.6

Cancer Chemother Pharmacol 2014;73(4):729-36

Docetaxel

Inhibitors	Half Life (Hours)	AUC (µg/h/ml)	AUC Fold Increase	Cmax (µg/mL)	Clearance (L/h/kg)
Docetaxel alone	6.4	**10.3**	-	18.1± 2.2	1.93
Plus ketoconazole	3.5	**31.4**	**3.1**	23.7 ± 2.1	0.64
Plus ritonavir	NR	**71**	**6.9**	43.5 ± 3.4	NR*

*NR: not reported due to > 50% extrapolation of the AUC due to poor terminal disposition rate constant

Cancer Chemother Pharmacol 2014;73(4):729-36

Bortezomib

- Prospective, multicenter, open-label, randomized, cross-over study
- 21 patients with advanced solid tumors
- Bortezomib was given 1 mg/m^2 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

Cycle		AUC (ng/ml/h) Mean (SD)
Cycle 1	Bortezomib alone	108 (25)
	Bortezomib + ketoconazole	137 (69)
Cycle 2	Bortezomib alone	171 (97)
	Bortezomib + ketoconazole	244 (83)

Clinical Therapeutics 2009;31:2444-2458

Bortezomib

Hematologic Toxicity		Bortezomib Alone Mean (SD)	Bortezomib + Ketoconazole Mean (SD)
Absolute Neutrophil Count (x 10^6/L)	Prior to Initiation	6.2 (3.8)	5.7 (2.0)
	Day 11	6.2 (5.0)	4.2 (2.1)
Hemoglobin (g/dL)	Prior to Initiation	12 (1.20)	11.9 (1.0)
	Day 11	11.7 (0.9)	11.6 (1.2)
Platelets (x10^9/L)	Prior to Initiation	291 (133)	311 (163)
	Day 11	212 (116)	223 (126)
White Blood Cell Count (x10^9/L)	Prior to Initiation	8.3 (4.1)	7.7 (2.0)
	Day 11	8.2 (5.4)	5.9 (2.0)

Clinical Therapeutics 2009;31:2444-2458

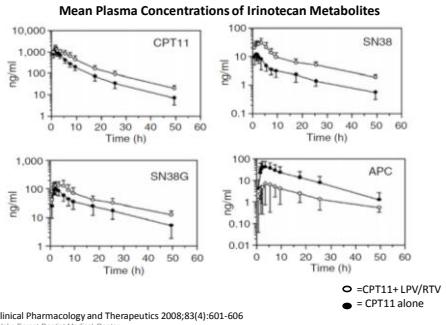
Irinotecan

- 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

Parameter	Irinotecan Alone (mean ± SD)	Irinotecan + LPV/RTV (mean ± SD)	P-Value
Cmax (ng/ml)	1,329 ± 310	1,594 ± 434	0.02
AUC (ug/L/h)	7,702 ± 2,205	14,334 ± 4,530	0.001
Clearance (L/h/m^2)	21.3 ± 6.3	11.3 ± 3.5	0.0008
Volume of Distribution at Steady State (L/h/m^2)	188 ± 54	131 ± 37	0.007

Clinical Pharmacology and Therapeutics 2008;83(4):601-606

Irinotecan



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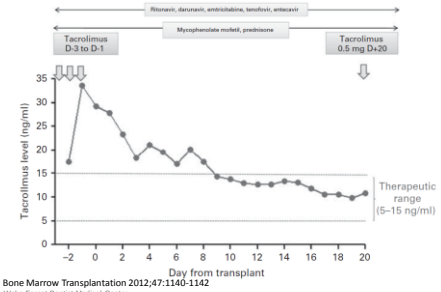
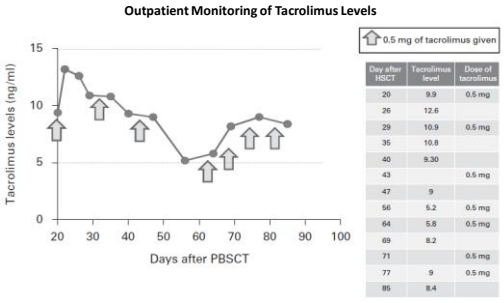
Tacrolimus

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



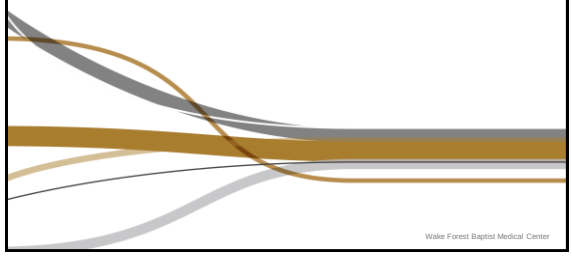
Bone Marrow Transplantation 2012;47:1140-1142

Tacrolimus



Bone Marrow Transplantation 2012;47:1140-1142

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

Summary

- 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

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References

- Abramowicz M. "Inhibitors and Inducers of CYP Enzymes and P-glycoprotein." The Medical Letter. 2013;55(1417):1-4
- American Cancer Society. "HIV infection, AIDS, and Cancer Detailed Guide." Last revised 7/5/2012
- Bundow D, Aboulagia D. "Potential Drug Interaction with Paclitaxel and Highly Active Antiretroviral Therapy in Two Patients with AIDS-Associated Kaposi Sarcoma." American Journal of Clinical Oncology 2004;27(1):81-84
- Cianfrocca M, Lee S, Von Roenn, et al. "Pilot study evaluating the interaction between paclitaxel and protease inhibitors in patients with human immunodeficiency virus-associated Kaposi's sarcoma: an Eastern Cooperative Oncology Group (ECOG) and AIDS Malignancy Consortium (AMC) trial. Cancer Chemother Pharmacol 2011;68:827-833
- Cingolani A, Torti L, Pinnetti C, et al. "Detrimental clinical interaction between ritonavir-boosted protease inhibitors and vinblastime in HIV-infected patients with Hodgkin's lymphoma." AIDS 2010;24(15): 2408-2411
- Cheung M, Hicks L, Leitch H. "Excessive Neurotoxicity with ABVD when Combined with Protease Inhibitor-Based Antiretroviral Therapy in the Treatment of AIDS-Related Hodgkin Lymphoma." Clinical Lymphoma, Myeloma, and Leukemia. April 2010:10(2);E22-E25
- Corona G, Vaccher E, Sandrom S, et al. "Lopinavir-Ritonavir Dramatically Affects the Pharmacokinetics of Irinotecan in HIV Patients with Kaposi's Sarcoma" Clinical Pharmacology and Therapeutics 2008;83 (4);601-606
- Engels F, Mathot R, Loos W, et al. "Influence of High-Dose Ketoconazole on the Pharmacokinetics of Docetaxel." Cancer Biology and Therapy 2006;5(7):833-839
- Ezzat H, Cheung M, Hicks L, et al. "Incidence, predictors and significance of severe toxicity in patients with human immunodeficiency virus-associated Hodgkin lymphoma." Leukemia and Lymphoma December 2012;53(12):2390-2396

References

- Grulich A, Van Leeuwen M, Falster M, et al. "Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis." Lancet 2007;370(9581):59-67
- Koolen S, Oostendorp R, Beijen J, et al. "Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer." Br J Clin Pharmacol 69;5:465-474
- Makinson, A, Pujol J, Moing V, et al. "Interactions Between Cytotoxic Chemotherapy and Antiretroviral Treatment in Human Immunodeficiency Virus-Infected Patients with Lung Cancer." J Thorac Oncol 2010;5:562-571
- Miceli M, Cronin S, Ayash L, et al. "Significant interaction of tacrolimus with ritonavir during allogeneic hematopoietic SCT in an HIV-infected patient." Bone Marrow Transplantation 2012;47:1140-1142
- Morbidity and Mortality Weekly Report from the CDC. "AIDS-Defining Conditions: Appendix A." December 5, 2008 57:10;1-12
- Panday V, Hoetelmans R, van Heeswijk R, et al. "Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma – drug-drug interactions with protease inhibitors and a non-nucleoside reverse transcriptase inhibitor: a case report study." Cancer Chemother Pharmacol 1999:43;516-519
- Rudek M, Chang C, Steadman K, et al. "Combination antiretroviral therapy (cART) component ritonavir significantly alters docetaxel exposure." Cancer Chemother Pharmacol 2014 Apr;73(4):729-36
- Venkatakrishnan, K, Rader M, Ramanathan R, et al. "Effect of the CYP3A4 Inhibitor Ketoconazole on the Pharmacokinetics and Pharmacodynamics of Bortezomib in Patients with Advanced Solid Tumors: A Prospective, Multicenter, Open-Label, Randomized, Two-Way Crossover Drug-Drug Interaction Study." Clinical Therapeutics 2009;31:2444-2458