Chemotherapy regimen: ABVD

Agents involved

• Doxorubicin	25 mg/m^2 IV	Day 1, 15
• Vinblastine	6 mg/m^2 IV	Day 1, 15
• Bleomycin	10 U/m^2 IV in 100 mL of NS	Day 1, 15
• Dacarbazine	375 mg/m^2 IV in 500 mL of NS	Day 1, 15

Summary

Antiretroviral agents to avoid

Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible [1-3]. *(Quality of Evidence: very low).*

If the patient is on one of the antiretroviral agents mentioned above, contact the HIV physician to request a change/substitution of antiretroviral agents.

Enzyme inhibition interactions[1]

- Possible increased vinblastine toxicity (*Quality of Evidence: moderate)*
  - Autonomic toxicity [5, 8, 9, 11]
  - Prolonged neutropenia [4, 8, 10, 11]

Enzyme induction interactions[2]

- Possible decreased efficacy of doxorubicin and vinblastine (*Quality of Evidence: very low;* theoretical, unknown clinical impact) [11, 12]

Enzyme neutral agents[3]: unlikely to interact

(*Quality of Evidence: very low*; theoretical)

- According to the metabolic profile of the individual agents, pharmacokinetic interactions are unlikely to occur. Nonetheless, additive toxicity remains possible with certain agents depending on the safety profile.

Laboratory interactions

(*Quality of Evidence: high*; no clinical significance)

- Cobicistat (Stribild®, Tybost®), rilpivirine (Edurant®, Complera®) and dolutegravir (Tivicay®) containing regimens will increase serum creatinine by approximately 7-15 µmol/L during the first 4 weeks of treatment initiation due to inhibition of renal creatinine secretion. This does not reflect an actual decrease in renal function and the effect is quickly reversible upon drug discontinuation.

Note: if interruption of any antiretroviral agent is considered necessary, contact the HIV physician to determine appropriate cessation of the antiretroviral therapy (certain antiretroviral regimens require sequential cessation of antiretroviral agents while others require immediate cessation of all antiretroviral agents at once). If treatment for hepatitis B (HBV) co-infection is required, consult the HIV physician, since some antiretroviral agents have activity against both HIV and HBV.

Literature

ABVD

A retrospective chart review of 16 HIV-infected patients with Hodgkin's lymphoma showed an **increased risk of grade III-IV neutropenia** (OR 34.3, 95% CI 1.9 – 602.4; p=0.02) when ABVD (n=13) or Stanford V (n=3) was administered with a PI-based combination antiretroviral therapy (cART) in comparison to a non PI-based cART. The authors also found an inverse correlation between ritonavir dose and mean nadir neutrophil count.[4]

Another retrospective chart review of 36 HIV-infected patients with Hodgkin's lymphoma evaluated the frequency and risk factors of ABVD (n = 29) or MOPP/ABV (n = 7) toxicity. Risk factors for **severe hematologic toxicity** were ritonavir (p=0.04) and lopinavir (p=0.02). Lopinavir use was also a risk factor for **increased grade 3 – 4 neurotoxicity** (p=0.05). [5]

Pharmacokinetic studies

Doxorubicin

Two studies evaluated the influence of cART on the **pharmacokinetics of doxorubicin** in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study reported **no significant difference** in doxorubicin pharmacokinetic parameters when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors [6]. Another study showed **similar clearance rates** of doxorubicin when administered with an indinavir-based cART [7]. No pharmacokinetic studies regarding interactions between antiretrovirals and bleomycin, vinblastine, dacarbazine were identified.

Vinblastine

One study evaluated the pharmacokinetics of vinblastine in 3 different patients who received atazanavir/ritonavir (300/100 mg daily), darunavir/ritonavir (600/100 mg daily) and lopinavir/ritonavir (300/100 mg BID) in the context of ABVD for treatment of Hodgkin's lymphoma. **Vinblastine area under the curve (AUC) was increased** by 131% and 101% when given with atazanavir and darunavir 600/100 mg once daily, respectively. This increase appeared to be well tolerated as both patients only reported WHO grade 2 toxicity (not specified). In contrast, when vinblastine was administered with lopinavir, vinblastine AUC was 1.6 fold higher than that achieved with atazanavir or darunavir and **resulted in paralytic ileus and febrile neutropenia**. [8] The increased toxicity observed with lopinavir may be due to the higher dose of ritonavir used (100 mg BID).

Case reports (Table 1)

A total of 4 published case reports [9, 10] were found regarding **excessive toxicity** when ABVD was co-administered with a PI based cART for treatment of Hodgkin's disease. All patients were treated with lopinavir/ritonavir, tenofovir and emtricitabine or lamivudine. One patient also received enfuvirtide. The authors suggested that vinblastine toxicity was due to decreased metabolism secondary to inhibition by lopinavir/ritonavir. This hypothesis is supported by another case report of excessive vinblastine toxicity when administered concomitantly with a lopinavir/ritonavir based cART for multicentric Castleman's disease. [11]

Table 1. Case reports of ABVD co-administered with a lopinavir/ritonavir based cART for treatment of Hodgkin's disease

Author	Description	Intervention	Outcome	Comments
Cheung 2010[9] Patient 1	Abdominal distension, obstipation (D7 cycle 1a)	Ileocolic resection and end ileostomy	uCR (24 months) after 6 cycles of ABD	No mention of hematologic toxicity (primary prophylaxis with GCSF)
Cheung 2010[9] Patient 2	Neutropenia	8 one-week delays, numerous dose reductions (not specified)	Remission 15 months post-diagnosis, narcotic dependent for neuropathy	Primary prophylaxis with GCSF
	Peripheral neuropathy	Narcotic use required Vinblastine omitted from cycle 5A onwards		
Cheung 2010[9] Patient 3	Febrile neutropenia (8 days after cycle 1a)	Broad spectrum antibiotics, GCSF, IV fluids	No further neutropenic delays	GCSF not used for primary prophylaxis
	Distension of small and large bowel	NG and rectal tube placed; vinblastine omitted from further cycles	No further ileus/obstruction	
	Bleomycin induced pneumonitis (cycle 5a)	Bleomycin omitted from future cycles	Not specified.	
Makinson 2007 [10]	Febrile neutropenia	Interruption of LPV/r 48 hours before and after chemotherapy	CR Adequate control of HIV	Increase of GCSF dosage and decrease of vinblastine dosage were also attempted but had still resulted in prolonged neutropenia.
Kotb 2006 [11]	Severe constipation, persistent pancytopenia (leading to septic shock), peripheral neuropathy	cART stopped: vinblastine administered at increasing doses (up to 6 mg/m^2) and well tolerated	Not specified	One dose of vinblastine was initially administered without cART and was well tolerated. cART was then resumed and resulted in increased toxicity during two concomitant administrations of vinblastine and cART.

Abbreviations: ABD (doxorubicin, bleomycin, dacarbazine); CR (complete response); GCSF (granulocyte colony stimulating factor); LPV/r (lopinavir/ritonavir); NG (nasogastric); uCR (unconfirmed complete response)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism [12, 13]	Possible interaction [12, 13]	Clinical evidence
Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives (inactive metabolites) conjugated to a sulfate or glucuronide metabolite. Enzymes of cytochrome P450 involved in free radical generation in vitro; substrate of PgP which may influence intracellular concentrations; clinical significance unknown.	Enzyme inhibitors may decrease reduction to free radicals via inhibition of cytochrome P450 which may decrease both antineoplastic and cytotoxic properties; however, they may also increase intracellular accumulation of doxorubicin via inhibition of PgP, which may enhance cytotoxic effects and/or systemic toxicity. Enzyme inducers may do the opposite.	No change. Doxorubicin pharmacokinetics (context of CHOP) not affected by PI administration.[6, 7]
Bleomycin	Hydrolysis by intracellular aminopeptidase. Evidence in rodents suggests possible inhibition of CYP450 system.	Possible increase of antiretroviral levels but potential for interactions appears low.	No studies or case reports found in the published literature.
Vinblastine	Metabolised by CYP 3A4. Vinblastine may also induce CYP3A4.	Possibility of increased levels (increased toxicity: autonomic, peripheral neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Increased risk of grade III-IV neutropenia [4] and neurotoxicity [5] with PI-based cART. Increased vinblastine AUC when given with boosted PI possibly resulting in increased toxicity. [8] 5 case reports reporting increased toxicity (with lopinavir/ritonavir).[9-11]
Dacarbazine	CYP1A2 > 2E1 to reactive DNA methylating metabolites.	Risk of interaction unlikely.	No studies or case reports found in the published literature.

Please consult http://hivclinic.ca/main/drugs_interact.html for more updated information.

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[1]Enzyme inhibitors include protease inhibitors (PIs): Crixivan® (indinavir), Invirase® (saquinavir), Kaletra® (lopinavir/ritonavir), Norvir®, Norvir sec® (ritonavir), Prezista® (darunavir), Reyataz® (atazanavir), Telzir® (fosamprenavir), Viracept® (nelfinavir); and the integrase inhibitor elvitegravir/cobicistat: available as a coformulated product with tenofovir/emtrictabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

[2]Enzyme inducers include non-nucleside reverse transcriptase inhibitors (NNRTIs): Atripla® (efavirenz/tenofovir/emtricitabine), Complera® (rilpivirine/tenofovir/emtricitabine), Edurant® (rilpivirine), Intelence® (etravirine), Sustiva® (efavirenz), Viramune®, Viramune XR® (nevirapine) and the protease inhibitor Aptivus® (tipranavir)

[3] Enzyme neutral agents include nucleoside reverse transcriptase inhibitors (NRTIs) : 3TC® (lamivudine), Combivir® (lamivudine/zidovudine), Kivexa ® (abacavir/lamivudine), Retrovir® (zidovudine), Trizivir® (abacavir/zidovudine/lamivudine), Truvada® (tenofovir/emtricitabine), Videx EC® (didanosine), Zerit® (stavudine); integrase inhibitors Isentress® (raltegravir), Tivicay® (dolutegravir); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)