

## Chemotherapy regimen: Hyper CVAD

### Agents involved

#### Cycle A

● Cyclophosphamide	300 mg/m <sup>2</sup> IV in 250 mL of NS	Days 1 – 3
● Dexamethasone	40 mg IV/po	Days 1 – 4; Days 11 – 14
● Methotrexate	12 mg IT	Day 2
● Doxorubicin	50 mg/m <sup>2</sup> IV	Day 4
● Vincristine	2 mg IV in 50 mL of NS	Day 4, 11
● Cytarabine	70 mg IT	Days 11

#### Cycle B

● Methotrexate	1000 mg/m <sup>2</sup> IV in 1250 mL of NS	Day 1
● Cytarabine	3 g/m <sup>2</sup> in 250 mL of NS q12h	Days 2 – 3
	If > 60 years old: reduce to 1.5 g/m <sup>2</sup> /dose	

### Summary of possible interactions with antiretroviral agents

#### Antiretroviral agents to avoid

- Avoid zidovudine-containing regimens (Retrovir®, Combivir®, Trizivir®) as additive hematologic toxicity is possible(1-3). (*Quality of Evidence: very low*)
- Avoid stavudine (Zerit®), didanosine (Videx EC®) due to possible additive peripheral neuropathy (4, 5). (*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<sup>1</sup>

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) (*Quality of Evidence: moderate*)
- Possible increased cyclophosphamide toxicity due to decreased clearance (8) (*Quality of Evidence: very low*; pharmacokinetic study of unknown clinical significance)

#### Enzyme induction interactions<sup>2</sup>

(*Quality of Evidence: very low*; theoretical, unknown clinical significance)

- Possible decreased efficacy of doxorubicin and vincristine (9, 10)
- Possible decreased efficacy and increase in cyclophosphamide toxicity due to increased inactivation to toxic metabolites (9, 10)

#### Enzyme neutral agents<sup>3</sup>: 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.

#### Particularities regarding nucleoside reverse transcriptase inhibitor backbone

(*Quality of Evidence: very low*; theoretical, unknown clinical significance)

- Potential additive renal toxicity with tenofovir (9, 10)

#### 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.

## Antiretroviral-Chemotherapy Interactions: Hyper CVAD regimen

### Literature

One study evaluated the use of hyper-CVAD for patients with HIV-associated Burkitt's leukemia/lymphoma. A total of 6/7 (86%) patients receiving a PI based cART achieved complete response and remained alive (median 29 month follow-up). HIV viral load remained undetectable for all adherent patients who received cART. For the 6 patients who did not receive cART during the entire chemotherapy treatment, 1 (17%) patient survived at 33 months follow-up with the use of cART (started after chemotherapy). The authors concluded that hyper-CVAD was highly effective within this context. Although no direct comparisons between patients receiving cART and those not receiving cART were made, they also stated that the use of cART with chemotherapy may be associated with a favorable outcome and that the administration of **cART was not associated with any identifiable increase in toxicity**. (11)

Data available from other regimens including similar antineoplastic agents are presented below.

### CHOP

One study evaluated the clinical impact of co-administration of cART with CHOP (**cyclophosphamide** 750 mg/m<sup>2</sup>, **doxorubicin** 50 mg/m<sup>2</sup>, **vincristine** 1.4 mg/m<sup>2</sup> [max 2 mg], prednisone 100 mg/m<sup>2</sup>) in the context of treatment for non-Hodgkin's lymphoma. In comparison to hyper CVAD, vincristine and cyclophosphamide doses per cycle are lower though doxorubicin dose is the same. They did not observe any difference in response rates, dose intensity or number of cycles of chemotherapy when CHOP was co-administered in 24 patients with a PI based cART (saquinavir, indinavir or ritonavir) in comparison to 80 patients on CHOP alone. They did observe, however, an **increased risk of grade 3 or 4 anemia and autonomic neurotoxicity** when CHOP was co-administered with a PI based cART in comparison to CHOP alone. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (7) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

### CDE

Several studies regarding the concomitant use of CDE (**cyclophosphamide** 1 200 mg/m<sup>2</sup>; **doxorubicin** 50 mg/m<sup>2</sup>; etoposide 240 mg/m<sup>2</sup> continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Cyclophosphamide dose is higher in comparison to hyper CVAD; however doxorubicin dose is the same. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based cART to those who received a non-PI based cART. The groups showed similar overall response and survival rates; however, an **increased risk of severe infections (48% vs 25%; p<0.01) and neutropenia (54% vs 38%; p =0.05)** was observed in patients on a PI based cART compared to those on a non-PI based cART(12). Another study in 12 patients showed an **increased risk of severe mucositis (67% vs 12%; p<0.01)** when patients received a saquinavir-based cART in comparison to a historical cohort not on cART(13).

### Pharmacokinetic studies

Two studies evaluated the influence of cART on the pharmacokinetics of doxorubicin 50 mg/m<sup>2</sup> in the context of CHOP for the treatment of non-Hodgkin's lymphoma. One study in 19 patients reported **no significant difference in doxorubicin pharmacokinetic parameters** when patients used saquinavir, nelfinavir or indinavir in addition to two nucleoside reverse transcriptase inhibitors (14). Another study in 29 patients showed similar clearance rates of doxorubicin when administered with an indinavir-based cART (8). The same study evaluated the pharmacokinetics of cyclophosphamide 750 mg/m<sup>2</sup> (lower dose than hyper CVAD) in the context of CHOP showed a **decrease of cyclophosphamide clearance** from 70 mL/min/m<sup>2</sup> to 41-46 mL/min/m<sup>2</sup> when administered with an indinavir-based cART. This however, did not translate into excessive toxicity. (8) Considering the higher dose used in hyper CVAD, closely monitor for increased cyclophosphamide toxicity.

### Case report

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, **doxorubicin** 40 mg/m<sup>2</sup> IV, **cyclophosphamide** 1600 mg/m<sup>2</sup> IV, **cytarabine** 140 mg IT, **methotrexate** 6720 mg/m<sup>2</sup> IV and **methotrexate** 15 mg IT per cycle) and lopinavir/ritonavir. The patient received one cycle of CODOX-M (**vincristine** 2 mg on D1 **and** D8) for treatment of Burkitt's lymphoma while on lopinavir/ritonavir based cART. Administered vincristine dose is identical to that administered with hyper CVAD. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m<sup>2</sup>; etoposide 300 mg/m<sup>2</sup>; **cytarabine** 8 g/m<sup>2</sup>) was administered with no complications though cytarabine dose is lower than that used in cycle 2 of hyper CVAD. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen was well tolerated and included similar doxorubicin dose and IT methotrexate dose; higher IV methotrexate, IV cyclophosphamide and IT cytarabine doses compared to hyper CVAD. (6)

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m<sup>2</sup>, **vincristine** 1.6 mg/m<sup>2</sup>, **cyclophosphamide** 748 mg/m<sup>2</sup>, **doxorubicin** 40 mg/m<sup>2</sup> continuous infusion over 4 days, prednisone 60 mg/m<sup>2</sup> daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Compared to hyper-CVAD, doxorubicin and cyclophosphamide doses are similar though the administered vincristine dose per cycle is lower. (15)

## Antiretroviral-Chemotherapy Interactions: Hyper CVAD regimen

### Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(9, 10)	Possible interaction(9, 10)	Clinical evidence
<b>Vincristine</b>	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral neuropathy, myelosuppression) with CYP 3A4 inhibitors. Possibility of decreased levels with 3A4 inducers.	Possible increased risk of autonomic neurotoxicity when administered with a PI based regimen. (6, 7) Good tolerability in 2 cases with lopinavir/ritonavir and DA-EPOCH for treatment of anaplastic large-cell lymphoma. (15)
<b>Doxorubicin</b>	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.(8, 14)
<b>Cyclophosphamide</b>	Transformation to active metabolite: CYP2B6, 2C19 Transformation to inactive and possibly toxic metabolites: CYP 3A4	Ritonavir, nelfinavir, efavirenz and nevirapine may increase the amount of active metabolites formed by induction of CYP 2B6 leading to increased efficacy and toxicity of cyclophosphamide. Inhibition of 3A4 may increase drug availability for hydroxylation route thereby leading to increased efficacy and toxicity of cyclophosphamide. Induction of CYP 3A4 may increase neurotoxicity.	Decreased clearance of cyclophosphamide when administered with protease-inhibitors. No excess toxicity observed.(8)
<b>Cytarabine</b>	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive toxicity with other agents such as tenofovir (renal toxicity).	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma (6)
<b>Methotrexate</b>	Almost all drug is excreted unchanged in urine.	Increased monitoring of renal function with concomitant tenofovir administration.	No methotrexate toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (6)

Please consult [http://hivclinic.ca/main/drugs\\_interact.html](http://hivclinic.ca/main/drugs_interact.html) for more updated information

## Antiretroviral-Chemotherapy Interactions: Hyper CVAD regimen

### References

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<sup>1</sup>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/emtricitabine (Stribild®); pharmacokinetic enhancer cobicistat (Tybost®).

<sup>2</sup>Enzyme inducers include non-nucleoside 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)

<sup>3</sup> 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), dolutegravir (Tivicay®); entry inhibitors Fuzeon® (enfuvirtide), Celsentri® (maraviroc)