

Chemotherapy regimen: CNS lymphoma High-dose methotrexate protocol

Agents involved

- | | | |
|----------------|--|----------------------|
| • Methotrexate | 3500 mg/m ² IV in 500 mL of D5W | Day 1 |
| • Vincristine | 1.4mg/m ² IV in 50 mL of NS | Day 1 (odd cycles) |
| • Procarbazine | 100 mg/m ² po qhs | Day 1-7 (odd cycles) |

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 interactions¹

- Possible increased vincristine toxicity (autonomic neurotoxicity) (6, 7) (*Quality of Evidence: moderate*)
- Possible increased procarbazine toxicity (8, 9) (*Quality of Evidence: very low; theoretical, unknown clinical significance*)

Enzyme induction interactions²

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

- Possible decreased efficacy of vincristine (8, 9)
- Possible increased toxicity of procarbazine (8, 9)

Enzyme neutral agents³: 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 (8, 9)

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

No studies or case reports specifically regarding high-dose methotrexate protocol and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CHOP

One study evaluated the clinical impact of co-administration of combination antiretroviral therapy (cART) with CHOP (cyclophosphamide, doxorubicin, **vincristine** 1.4 mg/m² [max 2 mg], prednisone) in the context of treatment for non-Hodgkin's lymphoma. In comparison to high-dose methotrexate protocol, the vincristine dose is the same; however it is given at each cycle unlike the current protocol. 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. No difference was noted in regards to leucopenia, thrombocytopenia, mucositis or nausea. (6) It is important to note, however, that 58% of patients receiving cART had zidovudine in their regimen, likely explaining the increased risk of anemia.

CODOX-M

One case report described **increased vincristine toxicity** in the context of co-administration of CODOX-M (**vincristine** 4 mg IV, doxorubicin 40 mg/m² IV, cyclophosphamide 1600 mg/m² IV, cytarabine 140 mg IT, **methotrexate** 6720 mg/m² 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 largely superior to that given with high-dose methotrexate protocol. On Day 12, the patient developed paralytic ileus which lasted for 10 days. Two weeks after recovery, IVAC (ifosfamide 7.5 g/m²; etoposide 300 mg/m²; cytarabine 8 g/m²) was administered with no complications. Two months after the first cycle, the patient was given CODOX-M; however, the vincristine component was changed to etoposide. This regimen, which included a higher IV methotrexate dose compared to the high dose methotrexate protocol, was well tolerated. (7)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (etoposide 200 mg/m², **vincristine** 1.6 mg/m², cyclophosphamide 748 mg/m², doxorubicin 40 mg/m² continuous infusion over 4 days, prednisone 60 mg/m² daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. Vincristine dose used is similar to that used in high-dose methotrexate protocol; however it was given at each cycle unlike the current protocol. (10)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (8, 9)	Possible interaction(8, 9)	Clinical evidence
Methotrexate	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. (7)
Vincristine	CYP 3A4	Possibility of increased levels leading to increased toxicity (peripheral and autonomic 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.(10)
Procarbazine	Transformation to active metabolites: CYP2B6, 1A	Inhibition of CYP1A or 2B isoenzymes may result in decreased efficacy of procarbazine. Induction of CYP1A or 2B6 by nelfinavir, tipranavir, efavirenz, nevirapine and ritonavir may potentially ↑ activity and/or toxicity.	No studies or case reports found in the published literature.

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

Antiretroviral-Chemotherapy Interactions: CNS lymphoma regimen

References

1. Retrovir. Product monograph. GlaxoSmithKline; 2009.
2. Combivir. Product Monograph. GlaxoSmithKline; 2007.
3. Trizivir. Product Monograph. GlaxoSmithKline; 2008.
4. Zerit. Product monograph. Bristol-Myers Squibb Canada; 2010.
5. Videx Ec. Product monograph. Bristol-Myers Squibb Canada; 2010.
6. Vaccher E, Spina M, di Gennaro G, Talamini R, Nasti G, Schioppa O, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. *Cancer*. 2001 Jan 1;91(1):155-63.
7. Leveque D, Santucci R, Pavillet J, Herbrecht R, Bergerat JP. Paralytic ileus possibly associated with interaction between ritonavir/lopinavir and vincristine. *Pharm World Sci*. 2009 Dec;31(6):619-21.
8. Antoniou T, Tseng A. Potential interactions between antineoplastics and antiretrovirals. In: Tseng A, Foisy M, editors. *Handbook of HIV drug therapy*. 2010 ed. Toronto 2010. p. 373-92.
9. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet*. 2005;44(2):111-45.
10. Nagajothi N, Dham SK, Gelfand Y, Sanmugarajah J. Treatment of AIDS-associated anaplastic large-cell lymphoma with dose-adjusted EPOCH chemotherapy. *J Natl Med Assoc*. [Case Reports]. 2007 Jul;99(7):799-801.

¹Enzyme 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®).

²Enzyme 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)

³Enzyme 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)