

Chemotherapy regimen: ESHAP

Agents involved

- | | | |
|----------------------|---|------------|
| • Methylprednisolone | 500 mg IV in 100 mL of NS | Day 1 |
| • Cisplatin | 25 mg/m ² IV in 500 mL of NS | Days 1 – 4 |
| • Etoposide | 40 mg/m ² IV in 250 mL of NS | Days 1 – 4 |
| • Cytarabine | 2 g/m ² IV in 250 mL NS | Day 5 |

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)

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 etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (Quality of Evidence: moderate)
- Possible increased methylprednisolone toxicity (6, 7) (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 etoposide and methylprednisolone (6, 7)

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

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

- Potential additive renal toxicity with tenofovir (6, 7)

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.

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: ESHAP Regimen

Literature

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

Cisplatin containing regimens

A retrospective single arm study evaluated the efficacy and safety of GDP (gemcitabine 2000 mg/m², dexamethasone 160 mg, **cisplatin** 75 mg/m² per cycle) for treatment of relapsed or refractory AIDS-related non-Hodgkin's lymphoma (NHL) when administered with **efavirenz**/lamivudine/zidovudine. The dose of cisplatin is slightly lower than that used in ESHAP. A total of 48 patients were included, of whom 21% had complete remission, 33% had partial remission; two-year overall survival was 71%. Regarding toxicity, 13% of patients required **dose reduction or elimination of zidovudine** in the HIV regimen due to leukopenia. Main grade 3/4 toxicities observed were anemia (8%), neutropenia (42%) and thrombocytopenia (58%). A total of 63% of patients had undetectable HIV viral load at the end of chemotherapy. The authors concluded that GDP was an effective salvage regimen with **tolerant toxicity** in patients with relapsed or refractory AIDS-NHL though further studies are warranted. (8)

Of note, low response to antiretroviral therapy is likely explained by previous exposure to **efavirenz**/lamivudine/zidovudine with a history of poor adherence in 71% of patients and dose reduction or elimination of zidovudine during chemotherapy in 13% of patients. This could contribute to development of HIV resistance and decreased efficacy of antiretroviral agents. Induction of efavirenz metabolism by dexamethasone may also have contributed to decreased antiretroviral efficacy.

A case report showed severe hematological toxicity secondary to cisplatin and gemcitabine when administered with atazanavir, ritonavir, tenofovir, lamivudine for treatment of lung cancer. The patient received one cycle of **cisplatin** 80 mg/m² and gemcitabine 2000 mg/m² and had grade 3 appetite loss, grade 4 platelet toxicity and neutrophils/granulocytes. Of note, cisplatin dose is slightly lower than that used in the ESHAP regimen. In the 3 subsequent cycles, cisplatin and gemcitabine doses were subsequently reduced to 60 and 1600 mg/m² respectively for 3 subsequent cycles, all of which were well tolerated. HIV viral load remained undetectable throughout the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (9)

Etoposide, cytarabine containing regimen

One case report described **good tolerability of IVAC** (ifosfamide 7.5 g/m², **etoposide** 300 mg/m² IV, **cytarabine** 8 g/m² IV per cycle) after severe vincristine toxicity during CODOX-M. Both etoposide and cytarabine doses used were largely superior to those used in ESHAP. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based combination antiretroviral therapy (cART). He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC was administered and was well tolerated. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated. (10)

Etoposide containing regimens

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m²; doxorubicin 50 mg/m²; **etoposide** 240 mg/m² continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is significantly higher in comparison to ESHAP. One study in 46 patients who received CDE for treatment of AIDS related lymphoma compared those who received a PI based combination antiretroviral therapy (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(4). 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(5).

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. (11)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (6, 7)	Possible interaction (6, 7)	Clinical evidence
MP	CYP 3A4	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers.	No studies or case reports found in the published literature.
Cisplatin	Main route of elimination is renal.	Pharmacokinetic interactions unlikely. Cisplatin induced nephrotoxicity may necessitate dosage adjustments for certain antiretroviral agents. Potential additive renal toxicity with tenofovir.	Possible increased hematological toxicity of cisplatin in a case report with atazanavir/ritonavir for treatment of lung cancer. (9) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (8)
Etoposide	CYP 3A4 (main); CYP 2E1, 1A2 (minor)	Possibility of increased levels with 3A4 inhibitors which may increase the risk and severity of mucositis, myelosuppression and transaminitis. Possibility of decreased levels with 3A4 inducers.	Increased risk of etoposide toxicity shown in CDE regimen and PI-based regimen (infections, neutropenia, mucositis). (4, 5). Good tolerability in three cases with lopinavir/ritonavir and either DA-EPOCH or CODOX-M/IVAC for treatment of non-Hodgkin's lymphoma or Hodgkin's lymphoma, respectively. (10, 11)
Cytarabine	Transformation to active metabolite by cytidine deaminase in the liver	Potential additive renal toxicity with other agents such as tenofovir.	No cytarabine toxicity reported in one case where CODOX-M/IVAC was administered with lopinavir/ritonavir for treatment of Burkitt's lymphoma. (10)

MP: methylprednisolone

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

Antiretroviral-Chemotherapy Interactions: ESHAP Regimen

References

1. Retrovir. Product monograph. GlaxoSmithKline; 2009(Accessed March, 2011].
2. Combivir. Product Monograph. GlaxoSmithKline; 2007(Accessed March, 2011].
3. Trizivir. Product Monograph. GlaxoSmithKline; 2008(Accessed March, 2011].
4. Bower M, McCall-Peat N, Ryan N, Davies L, Young AM, Gupta S, et al. Protease inhibitors potentiate chemotherapy-induced neutropenia. *Blood*. 2004 Nov 1;104(9):2943-6.
5. Sparano JA, Wiernik PH, Hu X, Sarta C, Henry DH, Ratach H. Saquinavir enhances the mucosal toxicity of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma. *Med Oncol*. 1998 Apr;15(1):50-7.
6. 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.
7. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet*. 2005;44(2):111-45.
8. Zhong DT, Shi CM, Chen Q, et al. Study on effectiveness of gemcitabine, dexamethasone, and cisplatin (GDP) for relapsed or refractory AIDS-related non-Hodgkin's lymphoma. *Ann Hematol* 2012;91:1757-63.
9. Okuma Y, Hosomi Y, Takagi Y et al. Long-term survival following metachronous intratumoral hemorrhage in an HIV-infected patient with lung cancer. *Int J Clin Oncol* 2010;15:515-8.
10. 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.
11. 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)