Chemotherapy regimen: Minibeam

Agents involved

• BCNU	60 mg/m^2 IV in 250 mL of D5W	Day 1
• Etoposide	75 mg/m^2 IV in 500 mL of NS	Days 1 – 4
• Cytarabine	100 mg/m^2 IV in 250 mL NS q12h	Days 1 – 4
• Melphalan	30 mg/m^2 IV	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 interactions[1]

- Possible increased etoposide toxicity (infections, neutropenia, mucositis) (4, 5) (*Quality of Evidence: moderate)*

Enzyme induction interactions[2]

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

- Possible decreased efficacy of etoposide (6, 7)

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.

Particularities regarding nucleoside reverse transcriptase inhibitor backbone

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

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

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 MiniBeam and antiretroviral agents were found. Data available from other regimens including similar antineoplastic agents are presented below.

CDE

Several studies regarding the concomitant use of CDE (cyclophosphamide 1 200 mg/m^2; doxorubicin 50 mg/m^2; **etoposide** 240 mg/m^2 continuous infusion over 4 days q4weeks) and antiretroviral therapy were available. Etoposide dose is significantly lower in comparison to MiniBeam. 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).

CODOX-M/IVAC

One case report described **good tolerability of etoposide and cytarabine** after severe vincristine toxicity. The patient received CODOX-M for the treatment of Burkitt's lymphoma while on a lopinavir/ritonavir based cART. He developed paralytic ileus that lasted 10 days. Two weeks after his recovery, IVAC (ifosfamide 7.5 g/m^2, **etoposide** 300 mg/m^2 IV, **cytarabine** 8 g/m^2 IV per cycle) was administered and was well tolerated. Comparatively to MiniBeam, etoposide dose is the same although cytarabine dose is significantly higher. Subsequent cycles of CODOX-M were administered with etoposide (dose not specified) replacing the vincristine component and was well tolerated. (8)

DA-EPOCH

Two cases described **good tolerability** of dose-adjusted EPOCH (**etoposide** 200 mg/m^2, vincristine 1.6 mg/m^2, cyclophosphamide 748 mg/m^2, doxorubicin 40 mg/m^2 continuous infusion over 4 days, prednisone 60 mg/m^2 daily for 5 days) when administered with lopinavir/ritonavir for treatment of anaplastic large-cell lymphoma. (9)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism (6, 7)	Possible interaction (6, 7)	Clinical evidence
BCNU	Spontaneous degradation. (10)	Pharmacokinetic interactions unlikely.	No studies or case reports found in the published literature.
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. (8, 9)
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. (8)
Melphalan	Spontaneous chemical degradation in plasma to inactive metabolites.	Pharmacokinetic interactions 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)