

Chemotherapy regimen: GDP

Agents involved

- Gemcitabine 1 g/m² IV in 250 mL of NS Day 1
- Cisplatin 75 mg/m² IV in 500 mL of NS Day 1
- Dexamethasone 20 mg po BID Days 1 – 4

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

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

- Possible increased dexamethasone toxicity (4, 5)
- Possible decreased efficacy of PIs (4, 5)

Enzyme induction interactions²

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

- Possible decreased efficacy of dexamethasone (4, 5)
- Possible decreased efficacy of NNRTIs (4, 5)

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 (4, 5)

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

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. 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. (6)

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 similar to that used in the GDP regimen but the gemcitabine dose is largely superior. 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 thorough out the course of chemotherapy. The patient had adequate response to therapy and was alive for 17 months at the time of publication. (7)

Metabolism of chemotherapy agents

Chemotherapy agent	Metabolism(4, 5)	Possible interaction(4, 5)	Clinical evidence
Gemcitabine	Intracellular activation of gemcitabine. Rapidly deaminated in the blood, liver, kidneys and other tissues. (8)	Pharmacokinetic interactions unlikely.	Possible increased hematological toxicity of gemcitabine in a case report with atazanavir/ritonavir for treatment of lung cancer. (7) No increased gemcitabine toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
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. (7) No cisplatin toxicity or decreased efficacy reported in a retrospective study with efavirenz. (6)
Dexamethasone	Substrate and inducer of CYP 3A4.	Increased risk of steroid related toxicity with CYP 3A4 inhibitors. Possible decreased efficacy with CYP 3A4 inducers. Dexamethasone may decrease levels of PIs and NNRTIs.	Possible decreased efficacy of efavirenz reported in a retrospective study. (6)

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

Antiretroviral-Chemotherapy Interactions: GDP 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. 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.
5. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. Clin Pharmacokinet. 2005;44(2):111-45.
6. 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.
7. 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.
8. Gemcitabine. Cancer Drug Information: Drug monographs for Health Care Professionals. Last revised Feb 2010. Available online: www.cancercare.on.ca. [Accessed March, 2011].

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)

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)