

A PEER-REVIEWED ARTICLE

Interactions between antineoplastic agents and ARV drugs

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Drug-drug interactions can be a serious complication of taking multiple medications and account for 3% to 5% of all in-hospital medication errors.¹ The consequences of drug interactions vary, ranging from excessive blood levels causing drug toxicities to therapeutic failures following sub-optimal blood levels. While the advent of highly active antiretroviral therapy (HAART) for the treatment of HIV infection has revolutionized HIV care, the immunosuppression caused by this disease still increases the risk of cancer illnesses among this population. HIV-infected patients are burdened by a higher prevalence of neoplastic diseases, and along with the presence of HIV-associated co-morbidities and opportunistic infections, remain targets for polypharmacy, which in turn leads to drug-drug interactions.

The elucidation and understanding of the cytochrome P450 enzyme system has allowed us to study and at the same time speculate, based on the CYP characteristics of each agent, upon the nature of the drug-drug interactions that may arise upon coadministration. Since both antineoplastic agents and antiretrovirals are substrates, inducers, or inhibitors of the cytochrome P450 enzyme system, interactions occur when these groups of medications are administered concurrently. This article will review current literature regarding these interactions, mostly between the HIV-1 protease, nucleoside, and non-nucleoside reverse transcriptase inhibitors and commonly-used antineoplastic agents.

Currently there are six major classes of HIV antiretroviral agents available for use in highly active antiretroviral therapy (HAART), namely: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase inhibitors (IIs), chemokine receptor (CCR5) antagonists. Since NRTIs, fusion and integrase inhibitors do not undergo hepatic metabolism through the cytochrome P450 (CYP450) enzyme system, their drug interaction profile is minimal. NNRTIs, PIs and maraviroc (a CCR5-antagonist) are extensively metabolized by the CYP system and so are highly susceptible to drug-drug interactions.² HIV-infected patients with additional cancer diagnoses receive numerous medications including antiretroviral agents, antineoplastics, drugs for supportive care, and medications for other co-morbidities or HIV/AIDS-associated opportunistic infections. Such patients are at risk for polypharmacy and drug-drug interactions.³ Serious adverse drug events often accompany drug-drug interactions that account for significant morbidity, damage to vital organs and sometimes death.^{4,5,6}

Despite the impact of combined antiretroviral therapy on HIV-related mortality, malignancies remain the second most common cause of death following HIV infection in developed countries.^{7,8} Whereas patients who receive antineoplastic agents along with their antiretroviral agents may achieve better responses and higher rates of survival than those who receive only antineoplastic therapy,⁹ the likelihood of clinically significant drug-drug interactions increases. This is mostly because, similar to many of the commonly used antineoplastic agents, both protease inhibitors and the non-nucleoside reverse transcriptase inhibitors are either substrates, potent inhibitors, or inducers of the cytochrome P450 (CYP) enzyme system. As a consequence, coadministration of these drugs could result in pharmacokinetic interactions that either increase or decrease serum concentrations, potentially affecting toxicity or pharmacodynamic interactions that may increase or decrease efficacy, potentially leading to unexpected and unpredictable results. This review will discuss major drug interactions that occur between antiretroviral agents and antineoplastic agents in HIV-infected patients. Where studies have not been carried out, knowledge of the metabolic pathways will enable providers to predict potential drug-drug interactions.

Overview of cancer treatment

Guidelines from the National Cancer Treatment Consultation Center and other expert bodies recommend that treatment of cancer include local tumor control through surgery and/or radiation therapy followed by use of antineoplastic agents in order to prevent reoccurrence or treat metastatic disease. Most significant innovations in the treatment of neoplastic diseases include the identification of tumor markers, biological response modifiers such as interleukins, interferons and monoclonal antibodies, further characterization of molecular oncogenes and signal transduction pathways inhibitors. Still others include the identification of potential tumor targets, further characterization of the activity and mechanisms of resistance, and the addition

of new agents within a therapeutic strategy.¹⁰ Evidence suggests that treatment of HIV-infected patients with non-AIDS-related malignancies may be more difficult than in the general population, since they may present with more advanced disease and may not tolerate therapy as well as HIV-negative patients¹¹.

Anal and colorectal cancer

In the treatment of colorectal cancer, the two topoisomerase inhibitors, topotecan and irinotecan, are usually combined with 5-FU as first-line therapy. However since irinotecan is a major substrate of both CYP 3A4 and CYP2B6, inhibitors of both enzymes such as ritonavir and atazanavir may increase its blood levels and lead to increased toxicities. Atazanavir may potentially increase blood levels of irinotecan following inhibition of the uridine diphosphate glucuronyl transferase (UGT) enzyme. Close clinical monitoring is suggested when such drugs are used with atazanavir.¹²

Cervical cancers

Currently cisplatin-based chemoradiation is standard of care for most patients with locally advanced cervical cancer but the five-year relative survival rate is only 57.7%. In a study with a median follow-up of three years during which patients with locally advanced cervical cancer treated with combination chemotherapy including gemcitabine plus concurrent radiation were compared to single-agent cisplatin with concurrent radiation, patients who received gemcitabine combination chemotherapy plus radiation had a progression-free survival of 74% compared to 65% for those on standard therapy.¹³ Since neuropathy is often associated with use of cisplatin, caution is advised. Some taxanes such as paclitaxel are not always recommended because of drug interactions that lead to toxicities or dose reductions.¹⁴

Non-Hodgkin lymphoma (NHL) and Hodgkin disease

Non-Hodgkin lymphoma is the fifth most common cancer in the United States, accounting for about 4% of all malignancies in both men and women. NHL is seen more commonly in the elderly, among men, and in whites. In the absence of immunosuppression, NHL patients can be treated by full-dose CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone-based regimen with or without rituximab); or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.¹⁵⁻¹⁷

Mechanisms of drug interactions

In order to predict the occurrence of drug interactions, an understanding of the classifications and mechanisms is essential. Two broad categories of drug interactions are recognized: pharmacokinetic and pharmacodynamic interactions.¹⁸

Interactions are described as pharmacokinetic when the action of one drug alters the serum concentration of another drug by altering any of the following processes: drug liberation, absorption, distribution, metabolism, and excretion (the LADME system). Pharmacokinetics is the study of drug action through these various processes.

Pharmacodynamic interactions are those that may alter the overall clinical response expected from use of the drugs, by altering their efficacy and often their toxicity. The interaction could be synergistic and mostly positive (e.g., the positive antiretroviral response seen when zidovudine is combined with lamivudine). Conversely, it can be antagonistic and mostly negative (e.g., the additive bone marrow suppression caused by combining zidovudine and ganciclovir; nephrotoxicity caused by combining cidofovir and amphotericin B; or the neuropathy caused by stavudine combined with didanosine.¹⁹ Most of the pharmacodynamic interactions between antineoplastics and HAART involve the reverse transcriptase inhibitors; zidovudine, for instance, will exacerbate the bone marrow suppression seen with most antineoplastic agents when administered concomitantly in cancer patients with HIV infection.²⁰

Metabolism of antiretroviral agents

Current recommendations for initiation of HAART in treatment-naïve patients by the Department of Health and Human Services Guidelines²¹ for the treatment of HIV-1 infection in adults and adolescents include two different strategies that offer similar efficacy but with different toxicity profiles and genetic barriers to resistance. Two nucleosides, tenofovir/emtricitabine or abacavir/lamivudine, may be combined in a once-daily pill to be administered with either efavirenz, the most potent of the non-nucleosides, or a ritonavir-boosted protease inhibitor that includes atazanavir, lopinavir, fos-amprenavir and saquinavir. CYP450 is the metabolic enzyme system responsible for the elimination of many drugs from the body.

Although numerous enzyme families within the CYP450 have been identified, CYP3A4 is involved in the metabolism of the majority of drugs currently on the market. Other isoenzymes commonly associated with drug

metabolism include CYP1A2, CYP2C9 and CYP2D6. Drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme. Decreased metabolism leads to higher drug levels and increases in the potential for drug toxicity. Induction of the CYP450 system results in an increase in the clearance of concomitant medications metabolized by the same enzyme and so leads to a decrease in drug concentration. Since the full effect of enzyme induction is based upon the time required for new enzyme synthesis and the half-life of the inducing agent, enzyme induction occurs more slowly than inhibition. Table 1 summarizes the routes of elimination of all antiretroviral agents along with their effects on the CYP450 enzyme system.

Interactions associated with the NRTIs

The six nucleoside reverse transcriptase inhibitors (NRTIs) currently licensed in the USA are zidovudine, didanosine, stavudine, lamivudine, abacavir and emtricitabine; tenofovir disoproxil fumarate is the sole nucleotide RTI (NtRTI). The NRTIs are neither eliminated by the CYP enzymes nor do they induce or inhibit CYP; drug interactions that relate to metabolism are minimal.⁴⁴ However, drug interactions with this class may occur through other mechanisms such as altered GI absorption, distribution of concomitant medications, exacerbation of hematological and other toxicities, or renal excretion.⁴⁵

Interactions between antineoplastic agents and antiretroviral drugs

Antineoplastic drug interactions are particularly important because of the narrow therapeutic indices and the inherent toxicities of drug used in oncology.⁴⁶ As many of these drugs undergo metabolism through the same CYP system as antiretrovirals, mostly as substrates, their efficacy and toxicity profiles may be affected. Table 2 characterizes the effects of antineoplastic agents and interactions with antiretroviral agents based on the CYP isoenzymes that mediate their metabolism.

Major interactions with alkylating agents cyclophosphamide and ifosfamide

The anticancer alkylating agents, cyclophosphamide and ifosfamide, are both prodrugs that undergo extensive metabolism catalyzed by the CYP450 enzyme system to yield both active (4-hydroxylated) and therapeutically-inactive but neurotoxic (N-dechloromethylated) metabolites.⁴⁷ Despite their structural similarity and similar metabolism, important differences exist in the metabolism of cyclophosphamide and its isomer, ifosfamide.⁴⁸ When used in the management of Hodgkin disease and non-Hodgkin lymphoma, cyclophosphamide is metabolized by two separate pathways. Hydroxylation by the CYP2B6 isoenzyme yields 4-hydroxy-cyclophosphamide (4-OH-CPA) which eventually decomposes to the active moiety, phosphoramide mustard. N-dechloromethylation, mediated by CYP3A4 isoform, yields the inactive dechloromethyl-cyclophosphamide and chloroacetaldehyde, which is associated with both neurotoxicity and urotoxicity.⁴⁹⁻⁵² Fortunately, approximately only 10% of an administered dose of cyclophosphamide undergoes n-dechloroethylation, thus minimizing the neurotoxic potential of this agent.⁵³ In contrast to cyclophosphamide, ifosfamide is administered as a racemic mixture of its two enantiomers, (R)-ifosfamide and (S)-ifosfamide, and is subject to stereoselective metabolism. While bioactivation of the drug to the hydroxyl metabolite occurs predominantly through the CYP3A pathway, the N-dechloroethylation is more complex as both enantiomers are substrates for the CYP3A and CYP2B6 isomers. Thus the incidence of neurotoxicity due to ifosfamide is greater than that due to cyclophosphamide.⁵⁴⁻⁵⁵

Pharmacokinetic studies with HAART and these two alkylating agents are largely non-existent. In one report of 40 patients with AIDS-related NHL treated with indinavir-based HAART combined with CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone), the clearance of cyclophosphamide was reduced 1.5 fold relative to historical controls.⁵⁶ In the majority of studies evaluating cyclophosphamide-based chemotherapy plus combination HAART, such combinations were clinically feasible and effective. In view of the higher rates of grades 3-4 anemia in patients with AIDS-related NHL receiving CHOP with HAART compared to patients receiving CHOP alone (33% versus 7%) as reported by Vaccher *et al.*,⁵⁶ vigilant monitoring is necessary when such combinations are administered.⁵⁷

Major interactions with taxanes (docetaxel and paclitaxel)

The taxanes are assuming an increasingly important role in clinical practice because of their activity against a large variety of cancers (breast, lung, bladder, prostate, ovaries, and Kaposi sarcoma in HIV infection). Several key studies have established the efficacy of paclitaxel for the treatment of AIDS-related KS, with reports of overall responses ranging from 56% to 71%.^{58,59,60}

Thus patients with AIDS-related KS may receive concomitant HAART and paclitaxel since HAART is often used for treatment of the HIV infection and as adjunct to the management of KS. In a recent report,

coadministration of ritonavir in 12 patients with solid tumors strongly enhanced the apparent bioavailability of docetaxel; based on this preliminary data, caution is essential when giving docetaxel with boosted protease inhibitors, while consideration for further development of a clinically applicable oral formulation of docetaxel combined with ritonavir now seems feasible.⁶¹

Metabolism of paclitaxel occurs through two isoforms of the CYP system, CYP2C8 and CYP3A4, with the main metabolite in humans, 6- α -hydroxypaclitaxel, being generated as a result of CYP2C8 activity while 3-phenylhydroxypaclitaxel, a secondary metabolite, is formed through CYP3A4.⁶²

Since CYP2C8 is the major enzyme involved in paclitaxel metabolism, interactions with PIs and delavirdine may not be clinically important since the inhibition of CYP3A still leaves the major metabolic pathway available. Pharmacokinetic interactions between paclitaxel and HAART are available to date only as case reports. In most of these reports where nevirapine and specific CYP-modifying antiretrovirals were used in different cycles of chemotherapy with paclitaxel, both the concentration-time-curves (AUCs), as well as peak plasma concentrations of paclitaxel, were only slightly reduced with concomitant HAART. Such differences were small and not likely to be of any clinical significance in this small series of only two patients receiving concomitant indinavir therapy.⁶³ In contrast to these, several others report severe paclitaxel-related toxicity when used with HAART.^{64,65} In two patients who received paclitaxel for the treatment of AIDS-related KS, initial combinations of paclitaxel with either nelfinavir- or indinavir-based HAART were reasonably tolerated but the subsequent initiation of combination HAART with saquinavir, delavirdine and didanosine was complicated with the development of severe mucositis and febrile neutropenia. Other reports were of combination therapy with paclitaxel and carboplatin in the treatment of an adeno-carcinoma of unknown origin where the patient experienced severe mucositis and fatal febrile neutropenia.^{66,67} All these reports serve as reminders of the vigilant monitoring necessary when taxanes are co-administered with HAART.

Docetaxel is biotransformed by the CYP3A4 pathway into at least four inactive metabolites. In the report of the two cases by Parameswaram and his group,⁶⁹ the variations of activity of this cytochrome constitute a predictive factor for severe neutropenia. To date, no human drug interaction studies have been carried out between docetaxel and HAART. Studies in mice showed that ritonavir increased the plasma levels of docetaxel by 50-fold;⁶⁸ such increases in plasma concentrations of paclitaxel have been confirmed in clinical reports.⁶⁹ Conversely, the ability of taxanes to modulate the CYP enzymes could potentially lead to changes in the pharmacokinetics of HAART, hence leading to either toxicities or treatment failure. In one case report, however, pharmacokinetic parameters of ritonavir, indinavir, saquinavir, and nevirapine were found not to have been modified by paclitaxel.⁷⁰ In view of the above, more prospective studies are necessary, and until then clinicians may consider therapeutic drug monitoring for all antiretroviral agents whenever HAART and taxanes may need to be coadministered.⁷¹

Major drug interactions with the vinca alkaloids (vinblastine, vincristine and vinorelbine)

Vinca alkaloids have a broad spectrum of activity against a large variety of hematological and solid neoplasms and so remain an important class of antineoplastic agents. Apart from their application in the management of cancers not traditionally associated with HIV, vinblastine, vincristine and vinorelbine have also been used in the treatment of several HIV-related malignancies.

Vinblastine has been used as part of several protocols for the management of Hodgkin disease in patients with HIV.^{72,73} In the same way, vincristine is often used as part of the chemotherapy regimen for the management of AIDS-related NHL.⁷⁴ Since the addition of HAART to the chemotherapy of NHL has been associated with higher rates of remission and improved survival,^{75, 76} use of combination HAART and chemotherapy is likely to increase in patients with AIDS and NHL, hence increasing the risk of drug interactions. One small study of vinorelbine as treatment for the management of AIDS-related KS resulted in a response rate of 43% (n=35).⁷⁷

Since vinca alkaloids are substrates of the CYP3A4 enzyme system, they are vulnerable to the effects of both PIs and NNRTIs when coadministered. More recent evidence suggests that CYP3A4 is also involved in the detoxification of vinca alkaloids since less vinca-mediated cytotoxicity was observed in cell lines expressing CYP3A4, hence inhibition of such metabolism would be expected to increase both the risk and severity of vinca adverse events, especially neurotoxicity and myelosuppression.^{78,79,80}

In a retrospective study reported by Vaccher *et al.*,⁵⁶ a significantly higher rate of grades 3-4 autonomic neuropathy was observed in patients with AIDS-related NHL receiving CHOP plus HAART compared to patients receiving CHOP alone (17% versus 0%; p value 0.002). This difference may be related to the inhibition of vincristine metabolism by HIV protease inhibitors since resolution of symptoms was observed following interruption of HAART and all patients had normal hepatic function.⁸¹

Enzyme inhibition following PI-HAART therapy may contribute to life-threatening drug interactions between

antiretroviral therapy and vinblastine, as described in other case reports. A case of profound neutropenia was observed in a patient with stage IVB Hodgkin lymphoma treated by doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy and lopinavir-ritonavir as part of HAART.⁸² In another case report, a patient with HIV-associated multi-centric Castleman disease presented with unexpected severe digestive and hematological toxicities when vinblastine was used in combination HAART that included zidovudine, lamivudine, abacavir, nevirapine and ritonavir-boosted lopinavir.⁸³ In view of the limited data regarding interactions between vinca alkaloids and antiretroviral agents, all patients should be monitored closely for adverse events and dosage adjustments made when necessary, especially in renal and hepatic impairment.

Major drug interactions with the anthracyclines (doxorubicin and daunorubicin)

Limited pharmacokinetic data are available for concomitant administration of antiretroviral agents and anthracyclines. In the study by Ratner and his colleagues where 40 patients with AIDS-related NHL were treated with modified or full-dose of cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) in combination with indinavir-based HAART, no changes in the clearance of doxorubicin were observed relative to historical controls.⁸⁴ In another report, Toffoli and colleagues showed that PI-based HAART has no significant effect on the pharmacokinetics of doxorubicin in 19 HIV-infected patients with NHL treated with CHOP with and without HAART.⁸⁵ The metabolic fate of daunorubicin appears similar to that of doxorubicin; the main route of doxorubicin metabolism is by generation of the inactive 13-hydroxy metabolite doxorubicinol by way of the aldo-ketoreductase enzyme. Both doxorubicin and doxorubicinol are subsequently metabolized by the NADPH-dependent cytochrome reductase to non-cytotoxic aglycones.⁸⁶ Though the CYP system was not the main route of metabolism for doxorubicin, it appears to be involved in the generation of the free radical species that is associated with cardiotoxicity.⁸⁷ The metabolism of liposomal doxorubicin is expected to be similar to that of free doxorubicin.

Major drug interactions between HAART and the epipodophyllotoxins (etoposide and teniposide)

The primary route of metabolism of etoposide and teniposide is the CYP3A4 enzyme and both CYP2E1 and CYP1A2 are minor pathways.^{88,89}

There is therefore the possibility of increases in concentrations with CYP3A4 inhibitors such as the HIV protease inhibitors and decreases in concentrations with CYP3A4 inducers such as phenobarbital, phenytoin and the non-nucleoside reverse transcriptase inhibitors. Such increases in etoposide concentrations may increase the risk and severity of mucositis, myelosuppression and transaminitis, while increases in teniposide may increase risk and severity of myelosuppression.⁹⁰

Data is available regarding the tolerability of etoposide in HIV-infected patients on chemotherapy. In the study by Sparano *et al.*, a higher incidence of severe mucositis was seen in 8 out of 12 patients with HIV-related NHL treated with CDE (infusional cyclophosphamide, doxorubicin and etoposide) and saquinavir mesylate compared with 3 of 25 patients in a previous study of CDE without saquinavir.⁹¹ However, a later study comparing patients with HIV-associated NHL treated with CDE before and after the use of HAART showed that patients treated in the HAART era have less chemotherapy-associated toxicity and improved survival.⁹²

Major interactions between the camptothecins (irinotecan and topotecan) and antiretroviral agents

Irinotecan is a prodrug whose conversion to the active metabolite SN-38 by carboxylesterases in the liver is necessary for its antineoplastic effect. A second enzyme, uridine diphosphate glucuronyl transferase (UGT), conjugates SN-38 to form the SN-38 glucuronide (SN-38G). The metabolism of irinotecan therefore involves several enzyme systems. Irinotecan is also converted by CYP3A enzymes to form two metabolites which possess little antitumor activity, the aminopentane-carboxylic acid (APC) and 7-ethyl-20-(4-amino-1-piperidino) carbonyloxycamptothecin (NPC). In a recent study on the pharmacokinetics of irinotecan and HAART,⁹³ the effect of lopinavir/ritonavir was studied in seven HIV-infected patients with KS. The clearance of irinotecan was reduced by 47% following coadministration of lopinavir/ritonavir leading to an 82% reduction of the AUC of the oxidized metabolite APC. Following the inhibition of UGT1A1 by lopinavir/ritonavir, formation of the SN-38G metabolite was inhibited.⁹⁴ Both of these led to an increase in the availability of irinotecan for conversion into SN-38. Despite a 50% decrease in dose, one of these patients had to discontinue irinotecan because of persistent grade 2 neutropenia.⁹⁵

Most of the first-generation PIs will inhibit human UGT1A1 *in vitro* in the order of atazanavir > lopinavir ≈ nelfinavir ≈ saquinavir > ritonavir > indinavir; these interactions may increase the risk of irinotecan-related toxicities.^{96, 97} When used in combination HAART, inhibition of CYP3A4 or UGT1A1 may increase risk and severity of myelosuppression, whereas induction of CYP3A4 or glucuronidation may decrease efficacy of the drug responsible for the conversion of only 2.5-3.5% of an administered dose to the active metabolite. Therefore

the clinical relevance of interactions with antiretrovirals that inhibit CYP3A4 would most likely be minimal.⁹⁸

It is currently hypothesized that CYP3A4 inducers such as nevirapine and efavirenz may be of greater clinical relevance because of an eventual increase in the active metabolite, N-desmethyl topotecan. Confirmation of this hypothesis needs further pharmacokinetic studies.

P-glycoprotein modulated interactions

P-glycoprotein (Pgp) is extensively distributed and expressed in the intestinal epithelium hepatocytes, renal proximal tubular cells, and the capillary endothelial cells comprising the blood brain barrier. They play a protective role by either limiting the uptake or enhancing the removal of a substrate.⁹⁹ In recent years, the role of the P-glycoprotein transporter as both a mediator of acquired multi-drug resistance in oncology and as part of an important detoxifying system has been recognized.^{100,101} Considerable overlap occurs between the tissue distribution and the substrates of the CYP system and the P-glycoprotein transporter. Many commonly used antineoplastic agents including the taxanes, vinca alkaloids, steroids, carboplatins, tamoxifen, isotopomerase inhibitors, and others are also substrates for Pgp. Since HIV-1 protease inhibitors are also substrates of the same system, modulation of this transport system could potentially affect the disposition of PI-antiretroviral drugs, while for the same reason the pharmacokinetics of antineoplastic agents can also be modified through modulation of Pgp by antiretroviral agents.¹⁰²

The potential for interactions between PIs and antineoplastic agents that are substrates for Pgp is defined by several *in vitro* observations. The efflux of paclitaxel and vinblastine from cells expressing Pgp were significantly inhibited by saquinavir, ritonavir and nelfinavir, thereby increasing the intracellular levels of these agents in one study¹⁰³ and free doxorubicin in another study.¹⁰⁴

Pharmacodynamic interactions

Pharmacodynamic drug interactions which occur when two or more drugs are given together are mostly responsible for the increased risk of toxicity associated with concomitant administration of HAART and antineoplastic agents. Such drugs may act synergistically to enhance a positive response (zidovudine and lamivudine giving a higher clinical response than each alone) or worsen adverse drug effects (didanosine and stavudine increasing peripheral neuropathy). Table 3 describes the highlights of these drug interactions. Numerous reports highlight several key pharmacodynamic drug interactions, such as the role of protease inhibitors in potentiating chemotherapy-induced anemia, zidovudine-combination HAART in increasing myopathy,¹⁰⁵ bone marrow suppression,^{106, 107} and other nucleoside antiretroviral agents in increasing peripheral neuropathy¹⁰⁸ when coadministered with antineoplastic agents.

Conclusion

Following the advent of HAART and the immunosuppression that occurs in both HIV and cancer, the need for coadministration of HAART and drugs for cancer has increased, placing patients at the risk of pharmacokinetic and pharmacodynamic drug-drug interactions due to polypharmacy. Current understanding of the true nature of these drug interactions is limited because the mechanisms and pathways of drug metabolism for many antineoplastic agents have not been fully characterized, mostly because knowledge of the nature and role of the CYP enzyme system was non-existent at the time most of these agents were licensed. Since PIs and NNRTIs modulate CYP enzymes, they affect the efficacy and toxicities of antineoplastic agents, many of which are also substrates of the same enzyme system, through alterations in the pharmacokinetics of these drugs following drug-drug interactions. Most interaction data are currently being extrapolated from animal model studies, *in vitro* pharmacokinetic studies, and case reports. There is therefore a need for more prospective data on drug-drug interactions between these two sets of agents. While waiting for further research studies, recognition of the narrow therapeutic indices associated with antineoplastic agents warrants close monitoring of patients for toxicity of agents undergoing CYP-mediated metabolism. In order to avoid toxicities and reduced efficacy, choice of antineoplastic agents that rely on the CYP system for bioactivation should be made after careful consideration of the role of antiretroviral agents as CYP enzyme modifiers. In this manner, many unnecessary pharmacokinetic and pharmacodynamic drug-drug interactions will be avoided. ♦

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