**CASE STUDY**

The Effect of Atazanavir on Doxorubicin Pharmacokinetics: A Case Report

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**Background:** With the increasing incidence of cancers in the HIV-infected population, a better understanding of the clinical effects of the coadministration of chemotherapy and antiretroviral medications needs to be known. Doxorubicin is a common chemotherapy agent and atazanavir is a common antiretroviral agent. Atazanavir can cause hyperbilirubinemia. Doxorubicin is dosed by total bilirubin levels as a result of its metabolism. If prescribers follow the recommended dose adjustment for doxorubicin and hyperbilirubinemia, it can result in subtherapeutic doses of doxorubicin and potentially unsuccessful therapeutic results.

**Objectives:** The goal of this case report was to determine the clinical and pharmacokinetic effects of the coadministration of atazanavir and doxorubicin in 1 patient.

**Discussion:** We examined a patient undergoing chemotherapy for breast cancer with doxorubicin and cyclophosphamide while also receiving antiretroviral therapy, including atazanavir, darunavir, ritonavir, tenofovir, and emtricitabine for her HIV infection. The pharmacokinetics of doxorubicin and the clinical outcomes for the patient were monitored. The patient had an increase in total bilirubin secondary to atazanavir, suggesting a 75% dose reduction of doxorubicin. Because she showed no other signs of hepatotoxicity, she was given a full dose of doxorubicin. The patient quickly developed febrile neutropenia, requiring a 10% reduction for subsequent cycles. She continued to have episodes of febrile neutropenia. The pharmacokinetic evaluation was performed on day 1 of cycle 3. The doxorubicin area under the curve (AUC)₀⁻₁₂ for this patient was between 616 µg*hr/L and 691 µg*hr/L compared with a previously reported AUC₀⁻₁₂ of 673 ± 205 µg*hr/L.

**Conclusion:** This is the first case report to assess the pharmacokinetic profile of doxorubicin coadministered with atazanavir in the setting of hyperbilirubinemia. The recommended dose reduction of doxorubicin based on total bilirubin was not necessary in this case, based on the associated pharmacokinetics and clinical outcomes.

AIDS-defining cancers, such as Kaposi’s sarcoma and non-Hodgkin’s lymphoma, have always disproportionately affected individuals infected with HIV. Since the introduction of antiretroviral therapy in 1996, the incidence of these cancers has decreased dramatically. However, with this decline, there seemed to be an increase in non-AIDS-defining cancers, such as cancers of the anus, liver, and lung, and Hodgkin’s lymphoma. Many studies have shown that by administering antiretroviral therapy to patients with AIDS-defining cancers, survival and response to chemotherapy can be improved. Despite the increasing risk of non-AIDS-defining cancers and the need to use antiretroviral therapy with chemotherapy to improve outcomes, little is still known about the drug–drug interactions between these 2 classes of medications. Many clinical decisions are centered on theoretical outcomes that are based on the pharmacology of each agent; however, very limited clinical data are available regarding the concomitant use of these medications.

One drug–drug interaction in particular involves the anthracycline, doxorubicin, and the frequently prescribed antiretroviral protease inhibitor, atazanavir. Atazanavir is known to increase total bilirubin levels, but the drug rarely causes hepatotoxicity. Doxorubicin is dosed based on the elevation of total bilirubin because...
The concomitant use of these medications could result in subtherapeutic doses of doxorubicin, leading to poor chemotherapy treatment outcomes. There are currently no pharmacokinetic or clinical studies on the coadministration of doxorubicin and atazanavir.

A biopsy revealed invasive grade III ductal carcinoma, and immunohistochemical (IHC) staining showed no expression of estrogen or progesterone receptors. HER2 was 2+ by IHC staining, but it was negative for gene amplification.

Our patient had a family history of breast cancer, including her mother, 2 sisters, and a maternal aunt, all of whom were diagnosed in their 30s or early 40s. After genetic counseling, the patient tested positive for the BRCA1 mutation. A bilateral mastectomy and sentinel lymph node biopsy were performed, which were consistent with stage Ia cancer (ie, TNM stage pT1c N0 M0). Adjuvant systemic chemotherapy was initiated 5 weeks after an uneventful surgery.

Taxanes, such as docetaxel, were avoided, because of the significant drug–drug interactions with antiretroviral therapy, specifically inhibitors of the cytochrome (CY) P450 3A4 (CYP3A4) enzyme, which metabolizes docetaxel. When docetaxel is administered with CYP3A4 inhibitors, such as antiretroviral protease inhibitors, increases in docetaxel concentrations can be seen, resulting in myelosuppression. Furthermore, although taxane-containing regimens, such as docetaxel and cyclophosphamide, showed superiority in the adjuvant setting compared with standard doxorubicin and cyclophosphamide given every 3 weeks, currently no data are available comparing the docetaxel plus cyclophosphamide regimen (given every 3 weeks) and the dose-dense doxorubicin plus cyclophosphamide regimen (given every 2 weeks).8,9

Based on the Cancer and Leukemia Group B (CALGB) 9741 clinical trial, doxorubicin plus cyclophosphamide, given in a dose-dense fashion with growth factor support, has been shown to be superior to an every-3-week schedule.10 After considering all of the data, dose-dense doxorubicin plus cyclophosphamide, given every 2 weeks for 4 cycles, was chosen for this patient.

Our patient had not had antiretroviral therapy for approximately 7 years before her malignancy diagnosis. After her diagnosis, it was determined that antiretroviral therapy would help optimize her chemotherapy, based on higher response and survival rates seen in patients with lymphoma when a combination of chemotherapy and antiretroviral therapy were given.2,3,7,11 Although the same has not clearly been seen in patients with breast cancer, it is known that chemotherapy can be cytotoxic and can cause more immunosuppression. To prevent the worsening of immune function with cytotoxic agents, the use of antiretroviral therapy can help boost a patient’s immune function before the initiation of chemotherapy.12

The patient’s previous antiretroviral therapy exposure included zidovudine, lamivudine, tenofovir, abacavir, indinavir, saquinavir, nelfinavir, nevirapine, and efavirenz. Only 1 genotypic resistance test was performed, which showed pan sensitivity to all antiretroviral medications; however, this test was performed while the patient was not taking any medications, and it was therefore unclear if mutations were hidden because of a lack of drug pressure. Because of the patient’s extensive antiretroviral medication exposure since her 1997 HIV diagnosis, she was prescribed a regimen accounting for common mutations, such as the M184V, that may have occurred but were not found on her previous genotype testing.

Case Report

A 46-year-old white woman presented to our hospital with a palpable right breast mass. Her medical history included HIV, which was diagnosed in 1997. The patient presented with no pain or nipple discharge associated with the breast mass. Her physical examination was remarkable for a 1.8-cm × 1.7-cm mobile right breast mass, with no skin changes or palpable axillary lymphadenopathy. A diagnostic mammography demonstrated a medium- to high-density, 24-mm, round mass at the 12:00 to 1:00 position of the right breast. An ultrasound of the breast and right axilla showed a 20-mm, round cystic mass (Figure, Panel A) and a nonspecific 18-mm lymph node with cortical thickening (Figure, Panel B).
Shortly after her malignancy diagnosis, the patient was prescribed antiretroviral therapy with atazanavir 300 mg, darunavir 800 mg, ritonavir 100 mg, and tenofovir/emtricitabine 300/200 mg administered orally and daily. Before starting the antiretroviral therapy, the patient’s CD4 cell count was 634 (28%) cells/mm³, her HIV RNA level was 356,571 copies/mL, her total bilirubin was 0.9 mg/dL, her aspartate aminotransferase (AST) was 100 U/L, and her alanine aminotransferase (ALT) was 73 U/L. After 3 months of antiretroviral therapy, her total bilirubin increased, secondary to atazanavir, to 3.8 mg/dL, whereas her AST and ALT levels normalized to 27 U/L and 14 U/L, respectively. Our patient was supposed to begin chemotherapy after these laboratory data became available; however, the increase in total bilirubin suggested a reduction in doxorubicin dose by 75% (15 mg/m²).

Knowing that atazanavir can increase unconjugated and total bilirubin, but not conjugated bilirubin, we evaluated our patient’s conjugated bilirubin concentrations and found that they were within normal limits (ie, 0.2 mg/dL to 0.5 mg/dL). We determined that the increase in total bilirubin could have resulted from atazanavir and was not a true representation of the patient’s liver function. Therefore, we gave her the standard doses of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²).

Growth factor support was given on day 2 of chemotherapy, and, on day 9, the patient developed febrile neutropenia that required hospitalization. Her absolute neutrophil count (ANC) nadir after this cycle was 250 cells/mcL for less than 12 hours, and her ANC was up to 900 cells/mcL within 24 hours. The total duration of severe neutropenia was 24 hours after cycle 1.

Because of her febrile neutropenia, a 10% reduction in doxorubicin dose was used in subsequent chemotherapy cycles; however, the febrile neutropenia continued after each cycle. After cycle 4, her nadir was 0 cells/mcL, with a total duration of 84 hours of ANC <1000 cells/mcL.

Given that (1) the duration of severe neutropenia after treatment with pegfilgrastim during breast cancer treatment with docetaxel and cyclophosphamide is 1.8 days, (2) the incidence of severe neutropenia ranges from 30% to 50% during doxorubicin and cyclophosphamide therapy, and (3) the incidence of febrile neutropenia ranges from 1% to 7% during treatment with doxorubicin and cyclophosphamide, it was determined that our patient’s neutropenia was within the range of acceptability for normal chemotherapy effects. In addition, these previously reported results do not indicate the number of patients infected with HIV; therefore, our patient may have had a more profound hematologic response to the myelosuppressive therapy because of her underlying immune suppression.
Additional toxicities (other than febrile neutropenia) identified in this patient included nausea, vomiting, and stomatitis; these were all grade ≥ 3 toxicities and were all manageable and consistent with a dose-dense doxorubicin plus cyclophosphamide regimen.

It should be noted that in addition to the chemotherapy, the patient received aprepitant 125 mg, ondansetron 16 mg, and dexamethasone 12 mg on the days of chemotherapy. She also received pegfilgrastim 1 to 2 days after each cycle of chemotherapy. Aprepitant is a weak inhibitor of the CYP450 2C9 and CYP450 2C19 enzymes, and a moderate inhibitor of the CYP450 3A4 enzyme, but it is not expected to alter the metabolism of doxorubicin, cyclophosphamide, or antiretroviral therapy; it is indicated before this chemotherapy administration.16 Dexamethasone and ondansetron are also not expected to alter chemotherapy or antiretroviral therapy metabolism, and are indicated as part of the chemotherapy regimen.17,18

**Gilbert’s syndrome is an inherited disorder that causes unconjugated hyperbilirubinemia. This hyperbilirubinemia is similar to that seen in patients with atazanavir-induced direct hyperbilirubinemia.**

**Pharmacokinetic Analysis of Doxorubicin**

For further evaluation of the interaction between atazanavir and doxorubicin clearance, a pharmacokinetic study of doxorubicin was performed on day 1 of cycle 3. It should be noted that even during the third cycle, the patient’s CD4 cell count was 487 (48%) cells/mm³, her HIV RNA level was 128 copies/mL, her total bilirubin was 1.3 mg/dL, her AST was 27 U/L, and her ALT was 19 U/L. The conjugated bilirubin remained normal (at 0.4 mg/dL) 6 days after the initiation of the third cycle of chemotherapy.

All samples obtained from the patient for pharmacokinetic analysis were drawn during routine clinical care visits with her oncologist. With the samples obtained, only limited pharmacokinetic analyses were able to be made.

For the doxorubicin analysis, 5 mL of blood were drawn in sodium heparin–coated tubes at 0.25 hours, 0.5 hours, and 3 hours after administration once informed patient consent was obtained. The blood was immediately centrifuged for 15 minutes and stored at approximately −80°C until the time of the analysis. Doxorubicin concentrations were determined using a high-performance reverse-phase chromatographic method based on a previously described method.19 The assay was linear and validated using the range of 10 ng/mL to 500 ng/mL.

Because increased doxorubicin area under the curve (AUC) has been linked to toxicities, such as myelo-suppression, we calculated the AUC for our patient using a linear trapezoidal algorithm with WinNonlin v5.2. Using the range of previously reported gamma half-lives of 13 to 50 hours, the AUC_{0-12} for our patient was predicted to be between 616 µg*hr/L and 691 µg*hr/L.20,21 The previously reported estimated doxorubicin AUC_{0-12} is 673 ± 205 µg*hr/L.13

Previous studies have shown that the concentrations of doxorubicin after a 20-minute infusion at doses of 50 mg/m² and 60 mg/m² were 109 ± 14 ng/mL, and 135 ± 34 ng/mL at 0.5 hours after the infusion.22 Although our patient’s concentration of 94.2 ng/mL is slightly lower than previously reported, we believe that this may be a result of the lower concentrations expected after a 30-minute infusion, which our patient received, versus a 20-minute infusion.

Another study showed that doxorubicin administered 0.5 hours and 24 hours before paclitaxel resulted in doxorubicin concentrations of 66.0 ± 18.7 ng/mL and 40.9 ± 13.6 ng/mL, respectively, 3 hours after administration.19 The concentrations observed in our patient were similar (54 mg/m²) to those previously reported for patients who were administered doxorubicin 50 mg/m² or 60 mg/m² (Table). Six months after our patient’s last chemotherapy cycle, she presented for her follow-up visit doing well and without any evidence of breast cancer recurrence.

**Pharmacology of Doxorubicin**

Doxorubicin is a first-generation anthracycline that has been in use for more than 40 years. It is effective in the treatment of a variety of tumors and AIDS-defining cancers.23-25 The clearance of anthracyclines relies primarily on the liver for metabolism and for excretion of the active compound and metabolites. Metabolism of doxorubicin occurs by a CYP-mediated pathway. Doxorubicin is metabolized to a doxorubicinol and to aglycones. The doxorubicin and doxorubicinol components are cytotoxic, unlike the aglycone metabolites, which can be cardiotoxic.11,20,25 Doxorubicin is eliminated primarily through biliary and fecal routes. Approximately 40% to 50% of a dose appears in the bile after 5 days. The pharmacokinetics of doxorubicin are linear.20

Elevated total bilirubin levels and aminotransferases have been reported to predict doxorubicin toxicity. The guidelines for doxorubicin dose reduction based on elevated total bilirubin levels were proposed in the 1970s.13 Since then, several studies have shown...
an inconsistent relationship between liver function and doxorubicin metabolism.26,27

Twelves and colleagues conducted a doxorubicin pharmacokinetic study in 24 patients with abnormal liver chemistries.28 Patients with an increased total bilirubin level between 1.75 mg/dL and 17.3 mg/dL did in fact have decreased doxorubicin clearance, but no clear relationship was established between the elevation in bilirubin and the extent of doxorubicin clearance reduction.28 This study, in addition to other studies that assess doxorubicin pharmacokinetics with liver function, used total bilirubin, AST, and ALT, but the studies do not mention the conjugated and unconjugated bilirubin levels and often already-assessed patients with known liver function abnormalities.26-28

Gilbert’s syndrome is an inherited disorder that causes unconjugated hyperbilirubinemia. This hyperbilirubinemia is similar to that seen in patients with atazanavir-induced direct hyperbilirubinemia. A case report of a 62-year-old man with large-cell non-Hodgkin’s lymphoma and Gilbert’s syndrome who received doxorubicin treatment showed that, at the time of doxorubicin initiation, the patient had a total bilirubin level of 2.1 mg/dL and an unconjugated bilirubin level of 1.9 mg/dL. According to the doxorubicin dosing guidelines, the dose should have been decreased by 50% because of the total bilirubin, but the patient was subsequently given full-dose doxorubicin with no secondary complications of neutropenia or mucosal toxicities.29

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<tr>
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<th>Doxorubicin Pharmacokinetics: Our Patient versus Reports in the Literature</th>
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<tbody>
<tr>
<td><strong>Our patient, 54 mg/m²</strong></td>
<td></td>
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<tr>
<td>Sample time, hr</td>
<td>Doxorubicin, ng/mL</td>
</tr>
<tr>
<td>0.25</td>
<td>176.9</td>
</tr>
<tr>
<td>0.5</td>
<td>94.2</td>
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<tr>
<td>3.0</td>
<td>51.7</td>
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<tr>
<td>Cmax, ng/mL</td>
<td>176.9</td>
</tr>
<tr>
<td>AUC0-3, µg*hr/mL</td>
<td>260.5</td>
</tr>
<tr>
<td>AUC0-12, µg*hr/mL</td>
<td>673 ± 205</td>
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AUC indicates area under the curve; Cmax, maximum plasma concentration.

The Role of UGT1A1

UGT1A1 facilitates the excretion of bilirubin from the body. Unconjugated bilirubin is a product of the metabolism of heme from hemoglobin. This bilirubin is not water soluble, which prevents its elimination into bile. Unconjugated bilirubin is bound to albumin and transported to the liver for conjugation to facil-
The Role of P-glycoprotein

P-gp has many functions, depending on the site of these proteins. Its major role in our patient’s case includes the effects of HIV-1 infection on P-gp, the potential drug–drug interactions through P-gp, and the effects of P-gp on this patient’s chemotherapy and cancer.

P-gp is a protein that is most often found on the mucosal surface of the gastrointestinal (GI) tract. Its function is to prevent uptake of toxic substances and to help eliminate those substances across the mucosa of the GI tract.

To our knowledge, this is the first case report to discuss the interaction between doxorubicin and atazanavir. The pharmacokinetics performed in this study show that further evaluation of liver dysfunction beyond total bilirubin may be necessary in patients concomitantly taking medications that could inhibit UGT1A1.

P-gp has long been studied in cancer, because this protein is highly expressed in certain human cancers, such as breast cancer. As a drug efflux pump, P-gp plays a vital role in the ability of chemotherapy to access the cells needed for these cancers.

Various studies have been performed to provide patients with chemotherapy and P-gp inhibitors to enhance chemotherapy sensitivity; however, mixed outcomes of this drug–drug interaction have led to controversy, and no consensus can be made. Patel and Tannock discovered that the use of P-gp inhibitors with doxorubicin only increased doxorubicin’s uptake in cells close to the blood vessels but might have decreased doxorubicin uptake in distal cells. As noted earlier, most protease inhibitors serve as a P-gp substrate and inhibitor. This could lead to erratic uptake of doxorubicin in patients receiving chemotherapy. Ritonavir is the most potent P-gp inhibitor, which our patient was receiving. Although previous studies that have evaluated the use of doxorubicin with P-gp inhibitors do not clarify the drug–drug interaction potential for our patient at this time, it may be considered a confounding factor.

Conclusions

It is generally understood that patients infected with HIV have an elevated risk of AIDS-defining cancers. Although the increase in effectiveness of antiretroviral therapy has resulted in a significant decline in AIDS-defining cancers, we have seen an increase in non–AIDS-defining cancers, such as breast cancer. Despite the known risk of malignancies in the HIV-infected population, little is known about the clinical effects of chemotherapy with concomitant antiretroviral therapy. To our knowledge, this is the first case report to discuss the interaction between doxorubicin and atazanavir. The pharmacokinetics performed in this study show that further evaluation of liver dysfunction beyond total bilirubin may be necessary in patients concomitantly taking medications that could inhibit UGT1A1 and subsequently increase total bilirubin concentrations, such as atazanavir. Furthermore, dose reduction of doxorubicin according to the total bilirubin level may not be appropriate when used in combination with inhibitors of both UGT1A1 and P-gp.

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Author Disclosure Statement

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References

The Effect of Atazanavir on Doxorubicin Pharmacokinetics