JPPT | Case Report

Severe Neuropathic Pain With Concomitant Administration of Vincristine and Posaconazole

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Vincristine is a chemotherapeutic agent with a potential toxicity of sensorimotor peripheral neuropathy. Patients receiving chemotherapy are in an immunocompromised state and may require antifungal agents. Triazole antifungals are known inhibitors of cytochrome P450 (CYP) enzymes. Vincristine is a known CYP3A4 and CYP3A5 substrate, and concomitant administration with fluconazole or voriconazole has been reported to increase vincristine toxicity and peripheral neuropathy, but there is limited literature on posaconazole in this regard. This 5-year-old girl with pre–B-cell acute lymphoblastic leukemia received vincristine while receiving posaconazole for a mucormycosis infection and developed unexpectedly severe peripheral neuropathy. After recovery, the child continued on mucormycosis prophylaxis with posaconazole with instructions to hold for 2 days before and on the day of vincristine administration. This case illustrates the potentiating effect that posaconazole had on vincristine-associated neurotoxicity, and our approach to mitigating that negative interaction.

ABBREVIATIONS ALL, acute lymphoblastic leukemia; CYP, cytochrome P450

KEYWORDS CYP3A4; leukemia; neurotoxicity; posaconazole; vincristine

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and is treated with chemotherapy. Vincristine is a key chemotherapeutic agent in regimens used to treat ALL. As a cell cycle–specific vinca alkaloid, it binds to tubulin and inhibits microtubule formation during mitosis and suppresses the proliferation of tumor cells. It is a major substrate of the cytochrome P450 (CYP) enzymes, specifically isoforms 3A4 and 3A5, and is also eliminated by P-glycoprotein, an efflux transporter.[1]

Triazole antifungals are often used for prophylaxis or treatment of fungal infections in ALL patients during chemotherapy. Posaconazole is a second-generation triazole antifungal agent that is an inhibitor of CYP3A4 and can potentially cause an increase in vincristine concentrations, leading to increased toxicities.[2] Several studies have documented the incidence of increased vincristine toxicities with concomitant use of other azole antifungals, such as itraconazole, voriconazole, and fluconazole.[3–5] There have been limited documented reports of the same increase in vincristine toxicities with posaconazole.[6,7]

We report a case of a child who received a dose of vincristine as part of her chemotherapy for pre–B-cell ALL with concomitant administration of posaconazole for a mucormycosis infection. This patient experienced unexpectedly severe toxicities with neuropathic pain and severe constipation from the coadministration of these 2 medications.

Case

A 5-year-old Hispanic girl weighing 18.5 kg received a diagnosis of high-risk pre–B-cell ALL and started on a 4-drug induction chemotherapy regimen (i.e., vincristine, dexamethasone, daunorubicin, and PEG-asparaginase) according to a Children's Oncology Group High Risk ALL Protocol (AALL1131). She was classified as high risk because of having received corticosteroids prior to diagnosis. Throughout her treatment all of the doses of vincristine were 1.5 mg/m^2 per dose. After achieving remission after 4 weeks of induction, she started on consolidation chemotherapy. Both these cycles of chemotherapy were completed without significant complications. She was planning to start interim maintenance 1 therapy with high-dose methotrexate and vincristine every 2 weeks for 4 courses; however, treatment was delayed because of febrile neutropenia. During the evaluation, she was found to have a lung nodule, which was biopsied, and the pathology was consistent with mucormycosis infection. She started a 6-week treatment with intravenous liposomal amphotericin (Ambisome, Gilead Sciences Inc, Northbrook, IL) 10 mg/kg/day and oral posaconazole 18 mg/kg/day divided every 8 hours, and underwent a right lower lobe resection.

Because of the severity of the infection and the toxicities involved in the treatment, high-dose methotrexate was deferred. Bridging maintenance chemotherapy modeled after the AALL1331 protocol (vincristine 1.5 mg/m^2 on days 1 and 22; 6-mercaptopurine 75 mg/m^2

on days 1–28; and methotrexate 20 mg/m^2 on days 1, 8, 15, and 22) was started while she was on liposomal amphotericin and posaconazole for treatment of mucor.

On day 6 of bridging maintenance (i.e., 5 days after vincristine was administered), she experienced new severe pain in right arm, chest, and jaw. The patient's gabapentin dose increased from 10 mg/kg/day to 20 mg/kg/day for neuropathic pain. She continued to experience jaw and arm pain for the next 2 days, requiring multiple doses of intravenous morphine. She developed severe foot drop, and she received physical therapy for ankle stretching exercises. The grade 3 peripheral motor/sensory neuropathy adverse effect was suspected to be secondary to vincristine and was thought to be potentiated by the interaction with posaconazole. Posaconazole was subsequently stopped on day 12 because of the unusually severe side effects from vincristine causing severe jaw and arm bone pain.

She also experienced severe constipation, with no bowel movements from days 6 through 10 of the bridging chemotherapy cycle. Prior to starting the vincristine on day 1 she had been receiving polyethylene glycol (8.5 g per dose) on an intermittent basis for approximately 2 weeks because of constipation, with 1 or 2 bowel movements each day on the 2 days immediately prior to the day 1 vincristine administration. The patient did not take all the polyethylene glycol doses even when offered it because she did not want to drink it. Her constipation worsened after the administration of vincristine for day 1 of the bridging chemotherapy. The constipation was likely exacerbated by the use of morphine for pain control. Gabapentin is associated with a low incidence of constipation also. Starting on day 5 of the bridging chemotherapy she received scheduled polyethylene glycol (8.5 g) twice a day and lactulose (10 g/15 mL) 4 times a day to promote bowel movements. On day 13, the day after posaconazole was discontinued, the patient had 6 bowel movements in a 24-hour period. She remained on liposomal amphotericin for the remaining 2 weeks of therapeutic antifungal treatment.

The patient was expected to receive intermittent vincristine for the remainder of her chemotherapy. Posaconazole was not an ideal option for long-term continuous use at treatment dosing because of the concerns for its increasing the neurotoxicity with vincristine. Consensus agreement was made between the family, the oncology team, and the infectious disease service to taper the liposomal amphotericin after a 6-week treatment to a prophylactic regimen of 10 mg/kg 3 times weekly for 4 to 6 weeks.

Outpatient liposomal amphotericin prophylaxis proved to be too logistically challenging of an option for the patient's family. A new plan was developed involving the use of posaconazole after completion of the patient's 6-week liposomal amphotericin treatment. Upon completion of 6 weeks of treatment with liposomal amphotericin, the patient was started on oral posaconazole 24 mg/kg/day divided 3 times a day with weekly posaconazole levels to reach a goal of ~3 to 4 mg/L. The next phase of chemotherapy (interim maintenance 1) included vincristine dosed at 2-week intervals with concomitant high-dose methotrexate. The first 2 doses of vincristine of interim maintenance therapy were held as 2 vincristine doses were given during the patient's bridging chemotherapy. This was expected to reduce the risk of interaction between posaconazole and vincristine, and to provide necessary mucormycosis prophylaxis.

The first posaconazole serum concentration came back at 0.48 mg/L, prompting investigation into administration of the oral suspension. The parents and nursing staff were educated to give posaconazole oral suspension after meals or with soda in order to increase the acidic environment for better absorption. The posaconazole dose was subsequently increased to 30 mg/kg/day divided 3 times a day with instructions to hold for 2 days before vincristine and on the day of vincristine administration. Using this approach of holding the posaconazole doses around doses of vincristine, she did not have severe neuropathic pain during interim maintenance, when the vincristine was only given every 14 days.

However, she did have recurrence of severe abdominal pain, back pain, and constipation during delayed intensification, which includes vincristine 1.5 mg/m^2 given weekly on days 1, 8, and 15, despite holding posaconazole for 48 hours before and on the day of vincristine administration. She had slowly been becoming more constipated and was using polyethylene glycol (8.5 g twice a day) and sennosides (8.6 g nightly) at home regularly, but starting on day 17 the stooling stopped for 4 days. She became symptomatic with abdominal pain on day 19 of delayed intensification, with hospital admission on day 21 for pain management. Upon admission, she received a larger dose of polyethylene glycol (17 g twice a day), and lactulose (20 g in 30 mL twice a day) was added. The constipation and abdominal pain symptoms resolved by day 26, and she was subsequently discharged home.

The patient has been in maintenance chemotherapy for 3 months at the time of manuscript preparation, and she receives vincristine every 4 weeks without recurrence of severe constipation or neuropathic pain. She continues to hold posaconazole for 48 hours before and on the day of vincristine administration. Her mild constipation and neuropathic pain have been managed with polyethylene glycol (8.5 g daily as needed) and sennosides (8.8 g twice a day as needed) for constipation, and gabapentin (15 mg/kg/day) for management of neuropathic pain. Throughout her treatment, despite her episodes of significant vincristine-associated neuropathic pain and constipation, there was resolution of the severe symptoms by the next due date for vincristine. Thus, although the protocol has recommendations for

dose reductions because of severe symptoms, she did not require dose reductions. Her ability to walk has improved, but she continues to receive physical therapy as of the writing of this manuscript, approximately 9 months after the original neuropathic pain episode with the concurrent administration of vincristine and posaconazole.

Discussion

This case report describes the development of increased neurotoxicity when vincristine is administered concomitantly with posaconazole. The specific toxicities experienced were peripheral neuropathy, gastrointestinal pain, and constipation. It should be noted that vincristine-induced peripheral neuropathy and constipation is a side effect that can occur in patients regardless of concomitant interacting medications and genetic predispositions.[8] However, patients with potential drug-drug interactions should be monitored more closely for increased toxicity.

Voriconazole-potentiating vincristine-induced peripheral neuropathy has been reported in the literature multiple times.[9,10] Vincristine is metabolized in part by the hepatic enzyme CYP3A4 and CYP3A5, which are both inhibited by voriconazole. Inhibition of this enzyme causes an increase in vincristine levels and may put the patient at risk of toxicities. Although drug interactions between vincristine and voriconazole have been reported in the literature, there have been limited reported cases of similar toxicities with posaconazole.

The different triazole antifungals have varying degrees of CYP inhibition, and thus can cause variable risks for vincristine toxicity. Administration of vincristine with either itraconazole or voriconazole was found to have higher rates of toxicity compared with fluconazole.[4] Posaconazole is structurally related to itraconazole and shares similar pharmacokinetic properties, including its strong inhibition of CYP3A4.[11] With the similarities between these 2 azole antifungals, posaconazole has the potential to increase the incidence of toxicities when given concomitantly with vincristine as well. The interaction between the two can cause higher serum concentrations of vincristine, resulting in increased toxicities seen similarly when voriconazole is given with vincristine.

The potentiating interaction between vincristine and posaconazole was witnessed in our patient's case during an overlap of therapy in which the patient experienced significant constipation, peripheral neuropathy, and jaw pain. Vincristine follows a triphasic serum decay pattern after intravenous injection, with initial, middle, and terminal half-lives of 5 minutes, 2.3 hours, and 85 hours. Thus, the initial high concentration of vincristine after infusion drops quickly, and then there is a prolonged, slow clearance at lower concentrations. The approximate half-life of oral posaconazole is 35 hours (range, 20–66 hours). Because of the long half-life, future doses of posaconazole for this patient are to be held 48 hours before vincristine and on the day of vincristine administration in order to minimize the risk of a drug-drug interaction for this patient. Morphine and gabapentin could also have contributed to the constipation.

There may also be genetic variants that predict the likelihood of a patient having vincristine-related peripheral neuropathy. Studies have demonstrated an association of an inherited polymorphism of the CEP72 promoter with an increased risk of neuropathy.[12] Adjusting the dose of vincristine in response to CEP72 variants is the subject of a current multicenter study, but changing vincristine dosing based on such findings is not currently the standard of care.

It is unclear what the effect of the holding the posaconazole intermittently would have on its efficacy for antifungal prophylaxis. Triazoles, such as fluconazole, itraconazole, voriconazole, and posaconazole, have concentration-independent fungistatic activity, and time-dependent and concentration-dependent fungicidal activities against different fungi.[13] If the dosing is appropriate, with a half-life of 35 hours, a steady-state level will be achieved in approximately 140 hours (4 half-lives) of starting the medication. Appropriate application of this information depends on what kind of fungi are prevalent in each patient's area and exposure history, and how frequently the vincristine is dosed.

This case report highlights the risk of coadministering posaconazole with vincristine and offers a potential regimen to decrease toxicities in the future. Particular caution should be observed with posaconazole because of the prolonged half-life. Measuring serum concentrations of posaconazole could be considered to ensure that residual inhibition of CYP3A4 is not present when vincristine is to be administered.

ARTICLE INFORMATION

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