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Letter to the Editor

Prolonged Vincristine Toxicity Induced by Concurrent Posaconazole in a Child with T-cell Acute Lymphoblastic Leukemia

Dear Editor,

An 8-year-old boy, a known case of T-cell acute lymphoblastic leukemia (ALL), was admitted for an episode of fever and neutropenia. In preliminary investigations and based on chest computed tomography results, he was diagnosed as having pulmonary fungal infection, which was treated with conventional amphotericin B. Two weeks later, chest computed tomography showed no improvement of the pulmonary nodules. Open lung biopsy was performed, and the culture of the biopsy specimen demonstrated aspergillus niger infection. Combined treatment with Caspofungin and Liposomal Amphotericin conferred clinical improvement, and the patient was discharged from the hospital after 3 weeks with oral Posaconazole. He was then scheduled to receive his maintenance chemotherapy based on the routine protocol, including vincristine (1.5 mg/m$^{2)}$, Doxorubicin (30 mg/m$^{2)}$, and 6-Mercaptopurine for 14 days and Prednisone for 5 days in the following week, after which he complained of severe jaw pain, disabling abdominal cramps, and obstipation for about 8 days. Plain abdomen radiography showed excessive intestinal gas without signs of obstruction, suggestive of paralytic ileus, which could be attributed to Vincristine toxicity. The prolonged interval between the Vincristine prescription and the presenting symptoms was, however, unusual. After 10 days of conservative management, the patient had persistent jaw pain without defecation as well as abdominal pain, which would decrease in forward position. Abdominal ultrasonography of the pancreas illustrated an increased echo pattern. Laboratory investigations only showed an increased serum lipase level and ESR but normal amylase level. Therefore, Posaconazole was discontinued, leading to the improvement of the symptoms within the next two days.

Vincristine is one of the main drugs in the treatment of children with ALL. Vincristine, as a vinca alkaloid, is metabolized by CYP3A. P glycoprotein also plays a major role in metabolizing this drug.[1,2]

Azole antifungal drugs are the cornerstones in the treatment of fungal infections in patients with leukemia. The main limiting factor in using such drugs in leukemic patients is that they interact with the normal metabolism of Vincristine by inhibiting CYP3A4. Furthermore, some azoles such as Ketoconazole and Posaconazole inhibit Vincristine transport by P-gp.[1] This may give rise to a higher probability of Vincristine toxicity in patients receiving both antifungal and Vincristine.

There are a few reports of Vincristine toxicity in patients receiving Posaconazole in the English language literature. Eiden,[3] reported severe peripheral neuropathy, abdominal cramp, and constipation in a young girl with ALL, who received combined Vincristine and Posaconazole. Central neuropathy presenting as the syndrome of inappropriate antidiuretic hormone (SIADH) by Vincristine toxicity has also been reported.[1] Hamdi et al.[4] reported seizure and SIADH in a young woman receiving Vincristine and Posaconazole. The presentation of our patient was very similar to what was reported by Eiden, but no central neuropathy was found in our patient. There is only another case of life-threatening neurotoxicity in a 4-year-old boy, who received Vincristine and Posaconazole for the treatment of ALL complicated with mucormycosis.[5] While the boy presented with persistent seizure as a sign of neurotoxicity, constipation was the common symptom between our case and the previous report. Mantadakis and colleagues,[6] reported a young adult, who received Vincristine and Posaconazole as prophylaxis. The authors also reported severe peripheral neuropathy as a side effect of such combined treatment.

The unique features of Posaconazole toxicity in our patient were jaw pain and ultrasonographic signs of pancreatitis. Pancreatitis has been reported as a drug reaction in the official drug information of Posaconazole; nevertheless, it has been reported in consequence of the other azole member, Itraconazole.[7] Another interesting point about our patient was the occurrence of these symptoms just after he had received one single dose of Vincristine; this has not been reported in the previous few reports.

Peripheral neuropathy manifesting as constipation and abdominal pain can present in patients receiving combined Vincristine and Posaconazole. Early diagnosis and conservative management are the only required managements needed in patients with ALL receiving both drugs. Not only should clinicians administering chemotherapy take heed of the interaction profile of Posaconazole with Vincristine but they should also closely monitor their patients for possible neurotoxicity.

Conflict of Interest: None declared.

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