Case Report

Itraconazole Induced Severe Vincristine Toxicities in Patients with Acute Lymphoblastic Leukemia

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Abstract: *Two patients with acute lymphoblastic leukemia (ALL) while receiving induction chemotherapy comprising of weekly injection of vincristine, doxorubicin and prednisolone had developed unusual severe vincristine toxicities. The events were due to drug interaction between vincristine and itraconazole which were given for antifungal prophylaxis. The symptoms spontaneously subsided after itraconazole withdrawal.*

Key Words : ● *Acute lymphoblastic leukemia* ● *Drug interaction* ● *Vincristine* ● *Itraconazole*

Thai J Hematol Transf Med 2002;12:35-8.

Systemic fungal infections (SFI) cause significant morbidity and mortality in neutropenic patients post intensive chemotherapy. Because of difficulties in diagnosing established SFI, antifungal prophylaxis is usually prescribed for patients undergoing this treatment.

Regarding medications used for antifungal prophylaxis, azoles can be given orally and are less toxic than intravenous amphotericin B. Among the azole group, ketoconazole is potentially hepatotoxic[1] while fluconazole has limited spectrum of activities especially against Aspergillus.[2, 3, 4] Itraconazole, a broad spectrum azole, has a wider spectrum of activities than fluconazole against aspergillosis[5, 6] but because of strong competitive enzyme inhibition of cytochrome P450 system, drug interaction is the major obstacle for achieving therapeutic goal. This communication reports two acute lymphoblastic leukemia (ALL) patients receiving vincristine-based induction chemotherapy and concomitant use of itraconazole in whom unusual severe vincristine toxicities developed. The mechanism of drug interaction is reviewed and discussed.

Received March 4, 2002. Accepted March 12, 2002.
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Case Report 1

A 34 year old female was referred from a private hospital with the diagnosis of acute leukemia. Her peripheral blood smear and bone marrow showed numerous lymphoblasts. Immunophenotype revealed pre-B ALL; cytogenetic analysis showed Philadelphia chromosome. At the private hospital, she developed jaundice, skin rash, lymphadenopathy and increase liver enzymes which were due to allopurinol hypersensitivity. She was treated with GMALL (German Multicenter Trials in Adult Acute Lymphoblastic Leukemia) induction chemotherapy protocol.[7] Dosages of vincristine and doxorubicin were decreased (vincristine 1 mg, doxorubicin 20 mg for the first week) and l-asparaginase was omitted due to abnormal liver function tests. Concomitantly she received itraconazole capsule 200 mg/day for antifungal prophylaxis.

After the second course of vincristine, she developed constipation and severe abdominal pain. Physical examination revealed distended abdomen and absence of bowel sound. Plain film abdomen revealed generalized bowel ileus. Serum electrolytes showed hyponatremia which was due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) (serum Na 133 mEq/L, serum osmolarity 267 mOsm/kg, urine osmolarity 673 mOsm/kg, uric acid 1.4 mg%). Vincristine induced paralytic ileus was diagnosed. Itraconazole was withdrawn and supportive treatment was given. Her symptoms improved 12 days later and further induction chemotherapy was given with vincristine and doxorubicin. No adverse toxicities were observed.

Case Report 2

A 17 year old girl diagnosed relapsed ALL was treated with weekly injection of vincristine, doxorubicin and prednisolone. The patient was taking itraconazole solution, 600 mg/day orally for suppression of cerebral aspergillosis which was developed one year earlier during the last phase IV chemotherapy.

After the second course of vincristine, the patient developed constipation and severe abdominal pain. Generalized bowel ileus on plain film abdomen was demonstrated. She was diagnosed vincristine induced paralytic ileus. Itraconazole was switched to liposomal amphotericin B. Her symptoms improved a week later after supportive treatment. Further vincristine was given without complications.

Discussion

Autonomic nerve dysfunction manifested as colicky pain, constipation and paralytic ileus was frequently reported in patients especially elderly patients receiving vincristine.[8, 9, 10, 11] Such complications were dose related, with greater frequency, severity and earlier onset in patients treated with higher doses.[10] Sandler et al reported mild abdominal pain and constipation in 23 out of 50 patients (46%) after receiving vincristine with 6 patients (12%) developed severe paralytic ileus.[11] Holland et al also reported constipation in one third of patients but

only 3 of 170 patients (1.76%) in whom highest dose (75 μg/kg/week) was given developed severe paralytic ileus requiring medical decompression.[10]

The occurrence of severe vincristine-induced paralytic ileus was rather unusual with the cumulative doses administered in these two patients (2 mg of vincristine in the first patient and 4 mg in the second patient). The most likely cause of severe bowel ileus in our patients was autonomic dysfunction due to drug interaction between vincristine and itraconazole. As itraconazole is extensively metabolized in the liver through cytochrome P450 system,[12] the elimination of vincristine is delayed and thus causing toxicities.

Previous reports documented cases of vincristine toxicities potentiated by itraconazole. Murphy et al reported five ALL children developed constipation, abdominal pain, hypertension, bowel ileus and hyponatremia while receiving vincristine containing induction chemotherapy and itraconazole 2.5 mg/kg/day.[13] Bohme et al reported the incidence of vincristine toxicity of 29% among patients receiving vincristine and itraconazole prophylaxis (itraconazole capsule, 400 mg/day) compared with 6% incidence in the previous 460 patients receiving the same chemotherapy regimen but without itraconazole.[14]

Systemic fungal infections, especially aspergillosis, cause significant detrimental effects in neutropenic patients. With conventional amphotericin B treatment, the mortality rate from pulmonary aspergillosis in bone marrow transplant recipient exceeds 94%.[16] Albeit its effectiveness for prevention of aspergillosis,[5, 6] drug interaction should be considered when itraconazole was used concomitantly with vincristine. These two patients in our report demonstrated the potential effect in enhancing the toxicities of vincristine by itraconazole. The concomitant use of these two drugs, whenever possible, should be avoided in clinical practice.

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ภาวะพิษจากยาวินคริสตีนซึ่งเกิดจากยาไอทราโคนาโซล ในผู้ป่วยมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบล้าสติก

พีระพล วอง และ ธานินทร์ อินทรกำธรชัย

หน่วยโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ: *รายงานผู้ป่วยมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบล้าสติก (acute lymphoblastic leukemia) 2 ราย เกิดภาวะพิษอย่างรุนแรงจากยาวินคริสตีน (Vincristine) ขณะเริ่มการรักษาด้วยยาเคมีบำบัด ซึ่งประกอบด้วยการให้ยาวินคริสตีน และด็อกโซรูบิซิน (Doxorubicin) ฉีดเข้าเส้นเลือดสัปดาห์ละครั้ง และเพรดนิโซโลน (Prednisolone) รับประทาน สาเหตุเกิดจากปฏิกิริยาระหว่างยาวินคริสตีน และยาไอทราโคนาโซล (Itraconazole) ซึ่งให้เพื่อป้องกันการติดเชื้อรา ผู้ป่วยมีอาการดีขึ้น และสามารถให้ยาเคมีบำบัดต่อได้โดยไม่เกิดอาการข้างเคียงจากยาวินคริสตีนอีก ภายหลังจากหยุดยาไอทราโคนาโซล*

Key Words : ● *Acute lymphoblastic leukemia* ● *Drug interaction* ● *Vincristine* ● *Itraconazole*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2545;12:35-8.