Clinical Analysis of Adverse Drug Reactions between Vincristine and Triazoles in Children with Acute Lymphoblastic Leukemia

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Background: Vincristine (VCR) is a major chemotherapy drug for treatment of childhood acute lymphoblastic leukemia (ALL). Triazole antifungal drugs (AFD) are the main agents for the prevention/treatment of invasive fungal infection (IFI), a common complication during the treatment of ALL. This study investigated the adverse drug reactions (ADRs) between VCR and AFD.

Material/Methods: A retrospective study was performed on 68 children with ALL (39 boys and 29 girls, median age: 5 years) who were treated with VCR chemotherapy (a total of 136 cases, including both induction and reinduction phases) from January 2012 to December 2013 in our hospital. These cases were divided into 4 groups: the control group without AFD prevention/treatment (n=44), the Itra group receiving itraconazole oral solution (n=44), the Fluc group receiving intravenous fluconazole (n=42), and the Vori group receiving voriconazole oral tablets (n=6). The ADRs in each group was recorded and compared.

Results: The incidence of ADRs in the Itra and Vori groups were significantly higher compared with the Fluc and the control group (P<0.05). The incidence of ADRs in the Itra group was significantly higher than that in the Vori group, whereas there was no difference in the incidence between the Fluc and control group.

Conclusions: Given the lower incidence of ADRs between VCR and fluconazole compared with voriconazole or itraconazole, it is relatively safer to use fluconazole in ALL patients receiving VCR chemotherapy. The occurrence of ADRs should be closely monitored when triazoles must be administered concomitantly with VCR.

MeSH Keywords: Drug-Related Side Effects and Adverse Reactions • Triazoles • Vincristine

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Background

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and poses a serious threat to the health of children. With the development of multi-drug combination therapy in the past 50 years, the efficacy in children with ALL has been significantly improved and the current cure rate is close to 80%. Vincristine (VCR) is one of the most commonly used chemotherapy drugs in the induction and consolidation phases during the treatment of ALL. VCR is an alkaloid extracted from the periwinkle plant of the Apocynaceae family, which has been gradually applied in the treatment of various tumors since 1963. VCR is a cell cycle-specific anticancer drug that stops microtubule formation during mitosis by inhibiting polymerization of tubulin, and thereby suppresses the proliferation of tumor cells. VCR is predominantly metabolized in the liver by the cytochrome P450 (CYP) superfamily of enzymes and eliminated by the efflux transporter, P-glycoprotein (P-gp) [1,2].

With the increasing dose-intensity of leukemia chemotherapy and broad-spectrum antibiotic therapy, invasive fungal infections (IFIs) have become highly prevalent in patients with ALL. IFI is the most common complication and cause of death in children with malignant tumors during chemotherapy. Triazole agents such as fluconazole, itraconazole, and voriconazole are the most common antifungal drugs (AFDs), and are effective for the prophylactic and therapeutic therapy for IFIs. However, adverse drug interactions (ADRs) with the combination of VCR and triazole AFDs have been previously reported, including gastrointestinal toxicity, peripheral neuropathy, electrolyte abnormalities, cranial neuropathy, and seizures [3–9]. These severe toxicities are presumed to be related to the inhibitory effects of triazole AFDs on the metabolism of VCR through the cytochrome P450 (CYP) superfamily of proteins and their transport by P-glycoprotein (P-gp). Despite numerous reports on the deleterious drug combination, little is known about the clinical manifestation, prophylaxis, and management of its ADRs, especially in Chinese patients. Furthermore, few reports with large sample sizes have compared the incidence of various toxicities caused by this drug combination [10]. In this study, we performed a retrospective analysis on a large number of cases (136 cases) in our hospital in the past 2 years, and provided a comprehensive summary of toxicities, clinical manifestation, outcome, and management of the ADRs between VCR and triazole AFDs.

Material and Methods

Subjects

A retrospective study was performed on 68 children (39 boys and 29 girls) who were diagnosed with ALL and treated with VCR chemotherapy from January 2012 to December 2013 in our hospital. The median age was around 5 years (1.5–14 years). Each patient was treated with both induction and re-induction chemotherapy using VDLD regimen (VCR, daunorubicin or doxorubicin, L-asparaginase, and prednisone or dexamethasone) resulting in a total of 136 cases of treatments. These cases were divided into the following 4 groups: the control group without AFD prophylaxis/treatment (44 cases), the Fluc group receiving itraconazole oral solution (44 cases), the Itra group receiving intravenous fluconazole (42 cases), and the Vori group receiving voriconazole oral tablets (6 cases).

Concomitant administration of AFD with VCR

In 62 cases of induction chemotherapy, 1.5 mg/m² VCR (a maximum dose of 2 mg) was administered intravenously to patients at day 1, 8, 15, 22, and 29 using VDLD regimen. Itraconazole oral solution was administered in 32 cases (2.5 mg/kg, q12h) and intravenous fluconazole in 30 cases (8 mg/kg, qd) starting from day 1 of VDLD therapy. In 30 cases of reinduction chemotherapy, 1.5 mg/m² VCR (a maximum dose of 2 mg) was administered intravenously to patients at day 1, 8, 15, 22, and 29 using VDLD regimen. Itraconazole oral solution was administered in 12 cases (2.5 mg/kg, q12h), intravenous fluconazole in 12 cases (8 mg/kg, qd), and voriconazole oral tablets in 6 cases (4 mg/kg, q12h) starting from day 1 of VDLD therapy. Patients in the Vori group had already been taking voriconazole oral tablets prior to reinduction phase due to the occurrence of IFIs during the consolidation phase of chemotherapy. The occurrence of ADRs was strictly monitored and the time from first dose of VCR to clinical manifestations of ADRs was recorded in each case. The medication of triazoles in a patient was immediately terminated after the ADRs were observed. Full or partial recovery from the ADRs was recorded in each case.

Statistical analysis

Statistical analysis was performed using SPSS18.0 software. Differences in the age distribution and in the time elapsed from first dose of VCR to onset of ADRs among all groups were analyzed by t-tests. Differences in the age distribution and in the incidence of ADRs among groups were compared by chi-square tests. P values smaller than 0.05 were considered to be statistically significant.

Results

Summary of subjects

A total of 136 cases of interactions with VCR were recorded for the following triazole AFDs: Itraconazole (n=44), fluconazole (n=42), and voriconazole (n=6). The median age for...
all patients was 5.2 years, with 30.9% of patients ≤3 years, 50% of patients 4–7 years, and 19.1% of patients 7–14 years. The age and sex distribution of the patients in all groups is summarized in Table 1, and no significant differences in the age and sex distribution were identified among these groups (P>0.05). The chemotherapy phase and purpose for concomitant administration of AFD with VCR in ALL patients are summarized in Table 2.

### ADRs between AFDs and VCR

The median time elapsed from the first dose of VCR to clinical manifestations of ADRs between AFD and VCR was 8.5 days (range, 6–14 days) with itraconazole, 18.9 days (range, 15–22 days) with fluconazole, 9.2 days (range, 5–16 days) with voriconazole, and 20.8 days (range, 17–23 days) in the control group, suggesting that ADRs in the Fluc group occurred significantly later than those in the other 2 experimental groups (P<0.05). In addition, the incidence of ADRs in the Itra group was significantly higher compared with the Fluc and the control groups (P<0.05). The incidence of ADRs in the Fluc and the control groups (P<0.05). Full and partial recovery from these ADRs occurred in 95.65% and 2.17% of cases, respectively, after the triazoles were discontinued. Death occurred in 2.8% of cases.

### Discussion

VCR is one of the main drugs for the treatment of acute lymphoblastic leukemia (ALL) and lymphoid malignancies in children. The metabolism of vincristine is mainly mediated by the CYP superfamily and the P-gp transporter. The CYP superfamily is a class of monoxygenases primarily located in the endoplasmic reticulum of cells, which is responsible for most drug metabolism in humans. The superfamily is divided into several subfamilies, including CYP3A4, CYP3A5, CYP2D6, CYP2C9, and CYP2C19. Of these, CYP3A4 is the most abundant CYP isoenzyme in the small intestine and in the liver [11], and accounts for over 50% of drug metabolism [12]. Despite its low

* Indicates P>0.05 in t-tests; ** indicates P>0.05 in chi-square tests using SPSS18.0 software.

### Table 1. The age and sex distribution of patients.

| Different AFD groups | Total |
|----------------------|-------|
| Itra group          | 44    |
| Fluc group          | 42    |
| Vori group          | 6     |
| Control group       | 44    |
| Total               | 136   |

| Median age * (range) | Total |
|----------------------|-------|
| 1–3 years            | 14    |
| 4–7 years            | 21    |
| 7–14 years           | 9     |
| Total                | 42 (30.1%) |
| Male/female**       | 26/18 |

### Table 2. Summary of chemotherapy phase and the purpose for concomitant administration of AFD with VCR in ALL patients.

| Different AFD groups | Total |
|----------------------|-------|
| Itra group          | 32/12 |
| Fluc group          | 30/12 |
| Vori group          | 0/6   |
| Total               | 62/30 |

| Prevention/treatment of IFIs | Total |
|------------------------------|-------|
| Itra group                   | 44/0  |
| Fluc group                   | 42/0  |
| Vori group                   | 2/4   |
| Total                        | 86/6  |
Table 3. ADRs between triazole AFDs and VCR.

|                     | Different AFD groups |                              | Control (n=44) |
|---------------------|----------------------|------------------------------|----------------|
|                     | Itra group (n=44)   | Fluc group (n=42)            | Vori group (n=6) | Total (n=92) |
| Total number of ADRs cases | 44 (100%)<sup>a</sup>| 11 (26.19%)<sup>b</sup> | 4 (66.67%)<sup>a</sup> | 59 (64.13%) | 13 (29.55%) |
| Gastrointestinal toxicity | 38 (86.36%) | 6 (14.29%) | 1 (16.67%) | 45 (48.91%) | 5 (11.36%) |
| Constipation/Abdominal pain | 38 (86.36%) | 5 (11.90%) | 1 (16.67%) | 44 (47.83%) | 5 (11.36%) |
| Vomiting | 24 (54.54%) | 1 (2.38%) | 0 | 25 (27.17%) | 0 |
| Ileus | 34 (77.27%) | 0 | 0 | 34 (36.96%) | 0 |
| Perforation | 1 (2.27%) | 0 | 0 | 1 (1.09%) | 0 |
| Hepatitis | 33 (75.00%) | 0 | 0 | 33 (35.87%) | 0 |
| Electrolyte abnormalities | 23 (52.27%) | 0 | 0 | 23 (25.00%) | 0 |
| Autonomic neuropathy | 21 (47.72%) | 0 | 0 | 21 (22.83%) | 0 |
| Hypertension | 8 (18.18%) | 0 | 0 | 8 (8.70%) | 0 |
| Difficulty urinating | 5 (11.36%) | 0 | 0 | 5 (5.43%) | 0 |
| Excessive sweating | 19 (43.18%) | 0 | 0 | 19 (20.65%) | 0 |
| Peripheral neuropathy | 26 (50.09%) | 1 (2.38%) | 2 (33.33%) | 29 (31.52%) | 0 |
| Back pain | 14 (31.81%) | 1 (2.38%) | 1 (16.67%) | 16 (17.39%) | 0 |
| Arthralgia | 8 (18.18%) | 0 | 1 (16.67%) | 9 (9.78%) | 0 |
| Limb weakness | 12 (27.27%) | 0 | 1 (16.67%) | 13 (14.13%) | 0 |
| Muscle spasm | 4 (9.09%) | 0 | 0 | 4 (4.35%) | 0 |
| Cranial neuropathy | 13 (29.54%) | 0 | 0 | 13 (14.13%) | 0 |
| Transient visual loss | 2 (4.54%) | 0 | 0 | 2 (2.17%) | 0 |
| Jaw pain | 7 (15.91%) | 0 | 0 | 7 (7.61%) | 0 |
| Ptoisis | 4 (9.09%) | 0 | 0 | 4 (4.35%) | 0 |
| Seizure | 8 (18.18%) | 0 | 0 | 8 (8.70%) | 0 |

- Time from first VCR dose to ADRs, median days (range): 8.5 (6–14) | 18.9 (15–22)<sup>*</sup> | 9.2 (5–16) | 10.1 (4–22) | 20.8 (17–23) |
- The number of VCR doses prior to ADRs: 2 (1–3) | 3 (2–4) | 2 (1–3) | 2 (1–4) | 3 (2–4) |
- Outcome of ADRs:
  - Full recovery: 40 (90.91%) | 42 (100%) | 6 (100%) | 88 (95.65%) | 44 (100%) |
  - Partial recovery: 2 (4.55%) | 0 | 0 | 2 (2.17) | 0 |
  - Death: 2 (4.55%) | 0 | 0 | 2 (2.17) | 0 |

<sup>a</sup> Indicates a significant difference from all other groups (P<0.05); <sup>b</sup> indicates a significant difference from the other experimental groups (P<0.05), but an insignificant difference from the control group (P>0.05). <sup>*</sup> Indicates a significant difference from the other experimental groups (P<0.05), but an insignificant difference from the control group (P>0.05).
toxicity to bone marrow, primary toxicity of VCR is neurotoxicity, which is dose-related and cumulative with repeated dosage [13]. Therefore, the metabolism of VCR by the CYP isoenzymes is important to prevent accumulation of the drug and its toxicity to the body.

Triazole AFDs interact with VCR by suppressing its metabolism through the CYP superfamily and the P-gp transporter [1, 2]. It has been found that itraconazole is primarily an inhibitor of both CY3A4 and P-gp [14, 15] due to its structure of a long hydrophobic arylaliphatic side chain, resulting in elevated plasma levels of VCR and aggravated toxicity. In contrast, fluconazole and voriconazole inhibit the activities of CY3A4, CY2C9, and CY2C19, without affecting the function of P-gp [14, 15]. These 2 drugs share a common structure of a substituted isopropyl group. Scholz and Moriyama et al. confirmed that voriconazole has a much greater inhibitory effect on CY2C19 compared with CY3A4/CY2C9, and thus interacts primarily with drugs that are metabolized through the CY2C19 pathway [16, 17]. Fluconazole is a weaker inhibitor of CY3A4 than itraconazole and voriconazole, and it inhibits the activity of CY3A4 in a dose-dependent manner [18]. As a result, conventional prophylactic doses of fluconazole may not induce ADRs in patients treated with vincristine. To date, there are few case reports on the ADRs between fluconazole and VCR [19–21]. In this study, ADRs occurred much more frequently in the Itra and Vori groups compared with the Fluc and the control groups (P<0.05). Furthermore, the incidence of ADRs in the Itra group was significantly higher than that in the Vori group (P<0.05), whereas there was no significant difference in the incidence of ADRs between the Fluc and the control groups (P>0.05). Our results were generally consistent with the pharmacological findings described above, although the result for voriconazole might be inaccurate due to the small number of cases in the Vori group and needs to be verified in further studies. Therefore, fluconazole can be used as a preventive antifungal drug during VCR chemotherapy. However, with the increasing incidence of fluconazole-resistant isolates [22], more in-depth studies should be performed to identify better antifungal drugs.

It has been previously reported that the toxicity of VCR is potentially determined by the cumulative doses of the drug [13]. Higher previous doses of VCR might potentially lead to more severe and frequent toxicity following an adverse reaction with an AFD [4, 10, 23, 24]. In this study, the incidence of ADRs in the Itra and Vori groups was significantly higher compared with the Fluc and the control groups (P<0.05), whereas the median number of VCR doses administered before the onset of ADRs was 2, 3, 2, 3 doses in the Itra, Fluc, Vori, and control groups, respectively, revealing no correlation between the cumulative doses of VCR and higher toxicity of the drug. However, further research shall be conducted on a larger number of cases to verify our observation.
Conclusions

In conclusion, with the increasing incidence of IFIs in children with ALL, it has become extremely important to choose an appropriate AFD for effective prevention and treatment of IFIs without causing serious drug interaction between AFD and the essential chemotherapy agent VCR. The ADRs of the combination of VCR and triazole AFDs should be strictly monitored and treated in a timely manner to prevent serious and potentially life-threatening consequences.

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