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ORIGINAL ARTICLE

Prophylactic administration of voriconazole with two different doses for invasive fungal infection in children and adolescents with acute myeloid leukemia

Hirozumi Sano*, Ryoji Kobayashi, Daiki Hori, Kenji Kishimoto, Daisuke Suzuki, Kazue Yasuda, Kunihiko Kobayashi

Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan

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KEYWORDS
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Abstract *Background:* Pediatric patients under treatment for acute myeloid leukemia (AML) are at high risk for invasive fungal infection (IFI). We evaluated the efficacy of prophylactic administration of voriconazole (VRCZ) with two different doses.
Methods: Between October 2005 and June 2011, 17 children and adolescents (aged 0–20 years) undergoing chemotherapy for AML were prophylactically administered with 5 mg/kg/d of oral VRCZ. Furthermore, 22 AML patients (aged 0–19 years) were administered 10 mg/kg/d of oral VRCZ between July 2011 and December 2014. The incidences of IFI with two different doses of VRCZ were compared.
Results: Irrespective of the dosage of VRCZ, eight patients developed IFI. Of these eight patients, four belonged to the 5 mg/kg/d group and four to the 10 mg/kg/d group. Cumulative incidences of IFI at 180 days after the initiation of chemotherapy were not different between the 5 mg/kg/d and 10 mg/kg/d groups. The trough plasma VRCZ concentration in the 10 mg/kg/d group ranged from < 0.09 μg/mL to 2.17 μg/mL, with a median level of 0.27 μg/mL, and patients with the targeted trough concentration (1–4 μg/mL) comprised only 18.8% of the evaluable patients in this group, whereas the trough plasma VRCZ concentration of the evaluable patients in the 5 mg/kg/d group were all below the limit of sensitivity (< 0.09 μg/mL).
Conclusion: More dose escalation is required based on this study. As VRCZ concentration is considerably influenced by genetic polymorphisms and drug–drug interactions, VRCZ should be used under therapeutic drug monitoring to keep effective drug concentrations.

* Corresponding author. Department of Pediatrics, Sapporo Hokuyu Hospital, Higashi-Sapporo 6-6, Shiroishi-ku, Sapporo 003-0006, Japan.
E-mail address: hirozumi.sano@gmail.com (H. Sano).

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Introduction

Recent developments of therapies including chemotherapy and hematopoietic stem cell transplantation (HSCT) have improved the survival of pediatric patients with hematologic and malignant disorders. Nonetheless, with intensification of therapy, such as multidrug chemotherapy and HSCT, there have been growing numbers of severe infections including invasive fungal infection (IFI). Patients with acute myeloid leukemia (AML) have been shown to be at high risk of IFI,[1–3] particularly invasive *Aspergillus* spp. infection (IA),[4] because of the intense myelosuppressive and immunosuppressive effects of their chemotherapeutic regimens. As the timely and accurate diagnosis of IFI during the course of chemotherapy is difficult, and because once it develops it is difficult to treat, prophylactic antifungal administration is important for high-risk patients.

Fluconazole has been widely used as the antifungal prophylaxis in cancer patients[5–8]; however, it has no effect on IA, *Candida krusei*, and other molds.[5,9,10] Voriconazole (VRCZ), a second-generation triazole, is effective against *Aspergillus* spp., and it has also been shown to be effective against other fungal pathogens, including some *Candida* strains intrinsically resistant to fluconazole. By contrast, compared with fluconazole, VRCZ may have greater toxicities[11–13] and drug interactions.[14,15] There have been a few trials concerning prophylactic administration of VRCZ for pediatric acute leukemia[16–18]; however, its effectiveness has not been well evaluated. Thus, we analyzed the efficacy of prophylactic VRCZ administration in pediatric patients with AML. We retrospectively compared the efficacy between VRCZ at a dose of 5 mg/kg/d and 10 mg/kg/d for the prevention of IFI.

Methods

Patients

A total of 39 consecutive patients with AML who underwent chemotherapy at Sapporo Hokuyu Hospital, Sapporo, Japan between October 2005 and March 2015 were enrolled in this study (every newly diagnosed or relapse-confirmed patient with AML in this period was enrolled). The patients were divided into two groups. Seventeen patients (9 boys and 8 girls, whose ages ranged from 0 years to 20 years, with a median age of 7 years) hospitalized between October 2005 and June 2011 were prophylactically administered with 5 mg/kg/d in two divided doses (maximal dose, 200 mg/d) of oral VRCZ starting at the beginning of chemotherapy. By contrast, 22 patients (10 boys and 12 girls, age range, 0—19 years, median age, 10 years) hospitalized between July 2011 and March 2015 were prophylactically administered with 10 mg/kg/d in two divided doses (maximal dose, 400 mg/d) of oral VRCZ.

Informed consent was obtained from the patients and/or their parents, according to guidelines based on the tenets of the revised Helsinki protocol. The Institutional Review Board of Sapporo Hokuyu Hospital approved this study.

Definitions of fever, neutropenia

Fever was defined as an axillary temperature of $\geq 37.5^{\circ}C$ on two occasions at least 1 hour apart or a single axillary temperature $\geq 38.0^{\circ}C$. Neutropenia was defined as an absolute neutrophil count of $< 0.5 \times 10^9/L$.

Infection prophylaxis, and treatment strategy against febrile neutropenia

All eligible patients were hospitalized in clean rooms of NASA class 10,000. Trimethoprim-sulfamethoxazole was prescribed to all patients for the prevention of *Pneumocystis jirovecii* pneumonia. The prophylactic administration of oral VRCZ at 5 mg/kg/d or 10 mg/kg/d was given as described above. Prophylactic administrations of antibacterial agents were not routinely performed. No construction work was performed in the ward during the study period.

When patients developed fever during neutropenia, the following laboratory tests were performed: complete blood cell count, peripheral blood smear, quantitative C-reactive protein (CRP), liver and renal function, urinalysis, and blood cultures from specimens obtained via peripheral venous puncture and/or a central venous catheter, if in place. Antibiotic therapy was begun as soon as possible without waiting for the blood culture results. The initial antibacterial drugs at the onset of fever were as follows: ceftazidime (CAZ) plus piperacillin/tazobactum (PIPC/TAZ) or sulbactam/ampicillin (SBT/ABPC) plus aztreonam (AZT) from June 1, 2004 to March 31, 2006[19]; CAZ plus PIPC/TAZ or cefozopran (CZOP) monotherapy from April 1, 2006 to March 31, 2008[20]; CZOP monotherapy or cefepime (CFPM) monotherapy from April 1, 2008 to March 31, 2010[21]; PIPC/TAZ monotherapy or CFPM monotherapy from April 1, 2010 to March 31, 2012[22]; and PIPC/TAZ monotherapy or meropenem monotherapy from April 1, 2012 to March 31, 2015 (data not published).

Initial antibiotics were continued when a case of fever was alleviated following initiation of antibiotics. In a case of fever continuing following initiation of antibiotics, or once resolved-fever and infectious signs subsequently recurring in spite of the continuation of the same antibiotic therapy, the laboratory tests including blood culture were performed again, and the antimicrobial therapy was changed to alternative antibacterial drugs or antifungal drugs.

Identification and definition of IFI

For prompt intervention against fungal infection, patients' blood samples were assayed for serum CRP by enzyme-linked immunoassay at least twice a week. When fever continued despite administration of broad-spectrum antibiotics and/or a high level of CRP persisted, computed tomography of the chest and abdomen was performed. In these patients, the detection of serum β-D-glucan and *Aspergillus* galactomannan antigen was also carried out.

IFI was defined and classified according to the standardized definitions from the European Organization for

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