Journal of Microbiology, Immunology and Infection (2018) 51, 260–266

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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

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Received 12 January 2016; received in revised form 16 March 2016; accepted 17 May 2016
Available online 2 June 2016

KEYWORDS
acute myeloid leukemia;
concentration;
invasive fungal infection;
prophylaxis;
voriconazole

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.

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http://dx.doi.org/10.1016/j.jmii.2016.05.002

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

Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycosis Study Group (EORTC/MSG) Consensus Group.[23] Proven IFI was diagnosed by a positive fungal culture from a normally sterile site. Probable IFI was diagnosed on the basis of a combination of host factors, clinical and radiological features, and mycological evidence, such as positive fungal culture or microscopy of bronchoalveolar lavage fluid or sinus aspirate. Possible IFI was diagnosed when the clinical and imaging findings, and host factors were consistent with IFI but there was no mycological evidence.

Analytic procedures

The primary hypothesis was whether VRCZ prophylaxis at 10 mg/kg/d would be associated with lower cumulative incidence of IFI after the initiation of chemotherapy for AML compared to that with 5 mg/kg/d. The incidences of proven, probable, or possible IFI during AML treatment were compared between two groups classified by VRCZ doses (5 mg/kg/d vs. 10 mg/kg/d). To evaluate the background of the enrolled patients, sex, age at hospitalization, cell morphology based on the French–American–British classification, and duration of VRCZ administration were also compared between the two groups. Trough plasma VRCZ concentration was not monitored routinely; however, it was evaluated in 22 out of 39 cases (6 of 17 cases in the 5 mg/kg/d group, and 16 of 22 cases in the 10 mg/kg/d group). Trough plasma VRCZ concentration was evaluated at least 7 days after initiation of VRCZ. Data were analyzed as of August 1, 2015.

Statistical analysis

A χ^2 test or Mann–Whitney *U* test was used to compare patients between the two groups. Cumulative incidence of IFI was assessed using the Kaplan–Meier method. Cumulative incidence of IFI, incorporating death as a competing risk, was computed for time from the initiation of chemotherapy to IFI. The Gray test was used to compare the two treatment arms. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.[24]

Results

Clinical characteristics

Irrespective of the prophylactic dosage of VRCZ, eight of 39 enrolled patients developed IFI (proven 1, probable 3, possible 4; Table 1). Of these eight patients, four belonged to the 5 mg/kg/d group and four to the 10 mg/kg/d group. Among them, *Aspergillus* sp. was the pathogen of IFI in two patients, one in the 5 mg/kg/d group, and one in the 10 mg/kg/d group. *Mucor* as the pathogen was found (1

Table 1 Eight patients who developed IFI despite voriconazole prophylaxis

Pt	Age (y)	Sex	FAB	Dosing period (d)	Preceding chemotherapy	IFI (EORTC/MSG)	Lesion (organ)	Predicted pathogen	VRCZ dose (mg/kg)	VRCZ concentration (μg/mL)	Outcome (cause of death)
1	16	M	M7 (relapse)	219	ECM, GO, FLAG, BHAC-AMP	Possible	Lung	gND	5	NA	Death (AML/IFI)
2	7	F	M2	118	ECM, HCEI, HCM, HCEI	Proven	Lung, brain	Mucor	5	NA	Survival
3	11	M	M4Eo	32	ECM	Possible	Lung	gND	5	NA	Survival
4	4	F	M7 (relapse)	28	FLAG	Probable	Lung	Aspergillus	5	NA	Death (AML/IFI)
5	11	F	M4	18	ECM	Probable	Lung	Aspergillus	10	0.24	Death (AML/IFI)
6	12	F	M4 (relapse)	71	FLAG–IDA, FLAG–IDA	Possible	Lung	gND	10	NA	Death (AML/IFI)
7	9	M	M2 (relapse)	118	ECM, HCEI, IDA–FLAG	Probable	Lung, brain	Mucor	10	NA	Death (AML/IFI)
8	17	M	M2	158	ECM, HCEI, HCM, HCEI	Possible	Lung	gND	10	0.21	Death (complication of HSCT)

AML = acute myeloid leukemia; BHAC-AMP = behenoyl cytarabine + aclacinomycin + 6-mercaptopurine + prednisolone; ECM = etoposide+cytarabine+mitoxantrone; EORTC/MSG = European Organization for Research and Treatment of Cancer/Mycosis Study Group; F = female; FAB = French–American–British classification; FLAG = fludarabine + AraC + granulocyte colony stimulating factor; gND = genus not defined; GO = gemtuzumab ozogamicin; HCEI = high dose-cytarabine + etoposide + idarubicin; HCM = high-dose cytarabine + mitoxantrone; HSCT = hematopoietic stem cell transplantation; IDA = idarubicin; IFI = invasive fungal infection; M = male; NA = not analyzed; Pt = patient; VRCZ = voriconazole.

patient in the 5 mg/kg/d group was a proven case) in two patients, each belonging to one of the groups. In the remaining four patients, genus of fungus could not be identified. Concerning the clinical characteristics, including age at diagnosis, sex, French–American–British classification, duration of VRCZ administration, and the reasons for discontinuation of VRCZ, there were no differences between the two groups (Table 2).

Comparison of antifungal effects

In terms of breakthrough infection rate, there were no differences between the two groups both in terms of the number of patient-based analysis [5 vs. 10 mg/kg/d, 23.5% (4/17) vs. 18.2% (4/22), $p = 0.709$] and the number of courses of chemotherapy-based analysis [7.3% (4/55) vs. 4.8% (4/84), $p = 0.712$]. The cumulative incidence of IFI at 180 days after the initiation of chemotherapy was similar between the 5 mg/kg/d (22.0%; 95% confidence interval, 0.0–41.4%) and 10 mg/kg/d (21.7%; 95% confidence interval, 0.0–8.7%) groups ($p = 0.552$; Figure 1).

Table 2 Comparison of characteristics between patients administered with 5 mg/kg/d and 10 mg/kg/d of voriconazole

VRCZ dose	5 mg/kg/d	10 mg/kg/d	*p*
No. of cases	17	22	
No. of courses of chemotherapy	55	79	
Age (y)	0–20	0–19	0.504
(median)	7	10	
Sex (male/female)	8/7	9/11	0.738
FAB classification			0.403
M1	3 (17.6)	1 (4.5)	0.300
M2	4 (23.5)	10 (45.5)	0.193
M4	1 (5.9)	4 (18.2)	0.363
M5	1 (5.9)	1 (4.5)	1.000
M6/RAEB	1 (5.9)	0	0.436
M7	6 (35.3)	5 (22.7)	0.482
(M7 with Down syndrome)	(0)	3 (13.6)	(0.243)
AML with MLD	1 (5.9)	1 (4.5)	1.000
Relapse of underlying disease	2 (11.8)	2 (9.1)	1.000
Dosing period (d)	10–230	3–233	0.802
(median)	126	158	
Reason for discontinuation of VRCZ			0.071
Completion of chemotherapy (AML)	4 (23.5)	9 (40.9)	0.318
Transition to HSCT	6 (35.3)	3 (13.6)	0.282
Febrile neutropenia (change to other drug)	2 (11.8)	0	0.436
Development of IFI	4 (23.5)	4 (18.2)	0.709
Death due to AML	1 (5.9)	1 (4.5)	1.000
Going on VRCZ	0	5 (22.7)	0.118
VRCZ concentration (μg/mL)	<0.09	<0.09–2.17	0.003
(median)	<0.09	0.27	

Data are presented as *n* (%), unless otherwise indicated.
AML = acute myeloid leukemia; FAB classification = French–American–British classification; HSCT = hematopoietic stem cell transplantation; IFI = invasive fungal infection; MLD = multilineage dysplasia; RAEB = refractory anemia with excess blasts; VRCZ = voriconazole.

Difference in concentration level of VRCZ

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 concentration of 0.27 μg/mL, and patients with the targeted trough plasma concentration (1–4 μg/mL) constituted only 18.8% of the evaluable patients, 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; Figure 2 and Table 2). Trough plasma VRCZ concentrations in two patients who developed IFI despite prophylactic administration at a dose of 10 mg/kg/d were low (0.21 μg/mL and 0.24 μg/mL; Figure 2). The trough plasma concentrations of the remaining six patients with IFI (4 patients in the 5 mg/kg/d group and 2 patients in the 10 mg/kg/d group) were not evaluated.

Adverse events in VRCZ prophylaxis

In both groups, there were no cases that required discontinuation of VRCZ because of adverse effects. No patients exhibited visual disturbances as an adverse effect of VRCZ.

Outcome following development of IFI

Among the eight patients who developed IFI, six patients died. In five of six patients (Nos. 1 and 4–7), treatments for underlying disease were postponed to resume and/or treatment intensity was reduced for fear of exacerbation of IFI under severe myelosuppression, which might lead to relapse or failure to achieve remission of underlying disease. Then, IFI rapidly increased possibly because of lack of

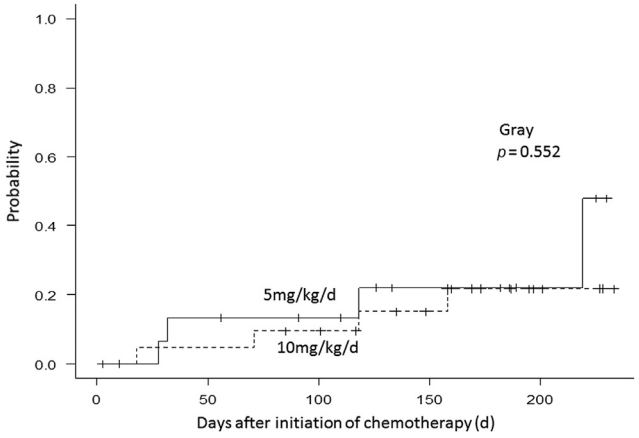

Figure 1. Cumulative incidence of invasive fungal infection in 39 cases with acute myeloid leukemia (AML). Kaplan–Meier estimates for patients treated with voriconazole at a dose of 5 mg/kg/d and 10 mg/kg/d are shown.

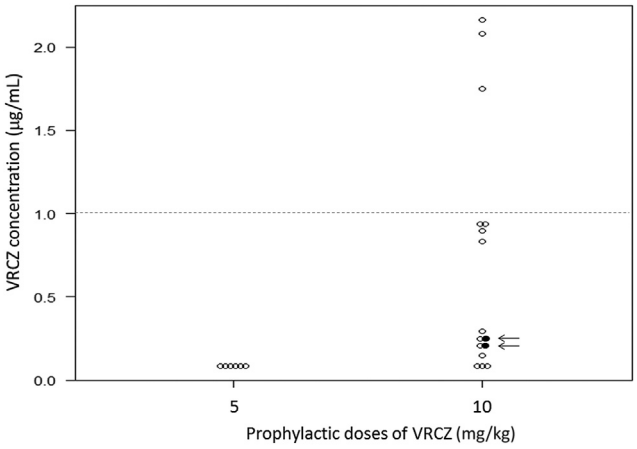

Figure 2. Distribution of plasma voriconazole concentration. Six of 17 cases treated with voriconazole (VRCZ) at a dose of 5 mg/kg and 16 of 22 cases treated with VRCZ at a dose of 10 mg/kg/d are analyzed for trough concentration of VRCZ. Closed circles with arrows represent two patients who developed invasive fungal infection (IFI) despite prophylactic use at a dose of 10 mg/kg/d. A broken line indicates the lower limit of the targeted VRCZ concentration.

antifungal immunity, leading to death. The remaining patient (No. 8) had once recovered from IFI, but died of complication of HSCT (Table 1).

Discussion

IFI is one of the most life-threatening complications in children and adolescents with hematologic and malignant diseases, especially AML.[1–4] Patients with IFI require antifungal agents, and sometimes chemotherapy is reduced to conserve their antifungal immunity for weeks to months, which may lead to the relapse of the original disease.[25] Moreover, the costs of prophylactic treatment were reported to be significantly lower than those for treatment of overt IFI.[18] Thus, prophylaxis for IFI in such high-risk patients is important.

VRCZ is an effective prophylactic agent in adult patients with AML[26,27]; however, only a few reports have been published regarding the prophylactic use of VRCZ for pediatric and adolescent AML patients.[16–18] These reports showed conflicting results. Maron et al[17] compared the frequency and outcome of invasive mold infection in AML patients prior to and after implementation of VRCZ prophylaxis, and concluded that VRCZ prophylaxis did not reduce invasive mold infections. By contrast, Yeh et al[18] reported a significant reduction of IFI in children with AML by comparing patients prior to and after the introduction of VRCZ prophylaxis.

One possible explanation for this difference in efficacy is the difference in the dosage of VRCZ. The VRCZ dose in the former report was 400 mg/d for patients weighing $\geq$ 40 kg, and 200 mg/d for those weighing $<$ 40 kg, whereas that of the latter report was 8 mg/kg/d. As a result, patients weighing 25–40 kg, and $\geq$ 50 kg in the former report received a lower dose of VRCZ than patients in the latter report. Although age distribution of the patients who developed IFI was not indicated in these studies, it is possible that lower doses of VRCZ in patients weighing 25–40 kg and $\geq$ 50 kg might lead to insufficient efficacy in prophylaxis of IFI. We used VRCZ at a dose of 5 mg/kg/d from October 2005 to June 2011, but we increased the VRCZ dose to 10 mg/kg/d starting in July 2011 and continued this strategy until March 2015. Thus, we examined if VRCZ at a dose of 10 mg/kg/d was superior to that of 5 mg/kg/d in preventing AML patients from developing IFI. However, there were no differences in cumulative incidence of IFI at 180 days after the initiation of chemotherapy for AML between patients receiving prophylactic VRCZ at a dose of 5 mg/kg/d and 10 mg/kg/d. The frequency of IFI in pediatric patients with AML has been reported to be 10–27%.[3,28] This wide range ensues because it tends to be influenced by various factors, such as environment of treatment/care, presence of construction work, diagnostic capability in each hospital, preceding chemotherapy, or antifungal prophylaxis. Although we cannot readily compare frequencies between different institutions, the frequencies of IFI in this study (23.5% in the 5 mg/kg/d group and 18.2% in the 10 mg/kg/d group) were considered acceptable.

An unexpected finding in this study was that the trough concentration of VRCZ was inadequately low even in patients with VRCZ at 10 mg/kg/d. Patients administered with 5 mg/kg/d so far all showed values below the limit of sensitivity. The pharmacokinetics of VRCZ has not been fully established, especially in the pediatric population. In children between the ages of 2 years and 12 years, the optimal dose may be 7 mg/kg twice daily,[29,30] whereas in children younger than 2 years, it may be as high as 8.5 mg/kg/dose twice daily.[31] Another report proposed a maintenance dose of 8 mg/kg twice daily for all children younger than 12 years, and for those 12–14 years of age weighing $<$ 50 kg.[32] At present, there is no consensus regarding the appropriate dose of VRCZ. Nevertheless, it is possible that the dose of 5 mg/kg/d or 10 mg/kg/d used in this study was not sufficiently effective against fungal infection. No adverse events concerning prophylactic use of VRCZ in this study could be explained by lower plasma VRCZ concentration. However, with regard to VRCZ dosage, there has been one interesting report that showed no advantage of 14 mg/kg/d over 10 mg/kg/d in prophylaxis efficacy and safety in children undergoing allogeneic HSCT.[33] VRCZ also has drug–drug interaction with many agents used in clinical practice, because it is a substrate of CYP2CP, 2C19, 3A4, and an inhibitor of 2C9, 2C19, 3A4.[34] For these reasons, therapeutic drug monitoring (TDM) is strongly recommended in clinical practice[31] to determine the optimal plasma VRCZ concentration.

The limitations of this study include its retrospective design, the small number of enrolled patients, and the fact that it is a single-institution study. Another is the fact that TDM of VRCZ was not routinely performed during the study period (especially low numbers of cases in patients with IFI), and polymorphisms that could influence plasma VRCZ concentration were not checked in this study. In addition, the concern about the existence of confounding factors caused by using historical control could not be eliminated. Nevertheless, the present study may provide valuable

information regarding the importance of plasma VRCZ concentrations in the prophylaxis of IFI.

In conclusion, no differences were observed between prophylactic VRCZ at 5 mg/kg/d and 10 mg/kg/d in the frequency of IFI. Lower plasma VRCZ concentrations even at the increased dosage may explain the lack of differences in IFI prophylaxis in the present study. When taking into consideration the antifungal spectrums of VRCZ, the prophylactic use of it is expected for the prevention of IFI in patients with AML, because they are at very high risk not only for candidiasis but also for mold infections, especially for IA. However, regarding dosage used for IFI prophylaxis, more dose escalation is required based on this study. Because VRCZ concentration is considerably influenced by genetic polymorphisms and drug—drug interactions, VRCZ prophylaxis should be done under TDM to maintain the effective and safe drug concentration. This strategy might be able to improve the risk of IFI in patients with AML.

Conflicts of interest

The authors have no conflicts of interest to declare.

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