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ORIGINAL ARTICLE

Impact of oral voriconazole during chemotherapy for acute myeloid leukemia and myelodysplastic syndrome: a Japanese nationwide retrospective cohort study

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Abstract

Background The prevention of invasive fungal infections is important in patients with acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) receiving cytoreductive chemotherapy. However, the role of oral voriconazole (VRCZ) in such patients has not been established. This study aimed to investigate the effectiveness of oral VRCZ compared to that of first-generation azoles prescribed within 7 days after the onset of chemotherapy in adult patients with AML/MDS using the Japanese administrative database.

Methods This nationwide retrospective cohort study was conducted using the Diagnosis Procedure Combination/Per-Diem Payment System. The primary outcome was the proportion of patients who switched to intravenous antifungal agents. Analyses using the instrumental variable method were performed to address unmeasured confounding.

Results In total, data on 5517 inpatients from 142 hospitals were analyzed. An oral VRCZ prescription was significantly associated with a reduction in the proportion of patients switching to intravenous antifungal agents compared to first-generation azole prescription (21.0% (95% confidence interval [CI] − 33.4 to − 8.6)). The impact of oral VRCZ in reducing the proportion of patients switching to intravenous antifungal agents was stronger in patients aged < 65 years than in those aged ≥ 65 years (− 40.6%, 95% CI − 63.2 to − 17.9; − 21.9%, 95% CI − 35.8 to − 8.1, respectively) and in patients prescribed oral azole within 3 days from the onset of chemotherapy than in those prescribed the same later (− 32.9%, 95% CI − 46.7 to − 19.2; − 9.0%, 95% CI − 33.7 to 15.7, respectively).

Conclusion Oral VRCZ administration may benefit adult patients with AML/MDS undergoing chemotherapy.

Keywords Invasive fungal infections · Acute myeloid leukemia · Myelodysplastic syndrome · Cytoreductive chemotherapy · Oral voriconazole

Introduction

The prevention of invasive fungal infections (IFIs) is important in patients with acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) during intensive chemotherapy.

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Current guidelines recommend the provision of antifungal prophylaxis for patients with AML/MDS who are expected to have long-term myelosuppression due to chemotherapy or hematopoietic stem cell transplantation (HSCT) [1–3]. The preventive role of voriconazole (VRCZ) following HSCT has been established [4–9]; however, the role of the prophylactic administration of oral VRCZ in AML/MDS patients receiving chemotherapy remains unclear.

Oral azoles such as fluconazole (FLCZ) and itraconazole (ITCZ)—so-called 'first-generation' azoles—are commonly used as prophylactic agents for IFIs in patients with AML/MDS receiving intensive chemotherapy [10–12]. Compared to these first-generation azoles, 'second-generation' azoles, including VRCZ, have an expanded antifungal spectrum, favorable bioavailability, and transferable formulation [2, 13–15]. Although the superiority of the therapeutic effect of VRCZ to IFIs compared to that of first-generation azoles has been reported, the benefits of the prophylactic administration of VRCZ in patients with AML/MDS undergoing chemotherapy have not been verified in a large-scale cohort. Guidelines recommend switching to a different anti-mold agent, administered "intravenously," for patients already undergoing prophylactic oral azole administration when a suspected IFI occurs [1, 2]; additionally, past studies have examined the effect of reducing the additional use of antifungal therapy between oral FLCZ prophylaxis and placebo [12], or between VRCZ and amphotericin B or FLCZ [12, 16]. However, it remains unclear whether oral VRCZ reduces the switching to intravenous antifungal agents more than first-generation azoles in patients with AML/MDS receiving intensive chemotherapy. In addition, the resulting shorter length of hospital stay and reduction in in-hospital mortality are also important clinical outcomes to be clarified.

In this study, we aimed to investigate whether early oral VRCZ prescription was associated with reductions in the use of intravenous antifungal agents, shorter lengths of hospital stay, and reductions in in-hospital mortality among adult patients with AML/MDS receiving intensive chemotherapy under aseptic management using a Japanese nationwide administrative database.

Patients and methods

Data source

This retrospective cohort study was conducted based on information collected from July 2010 to March 2015 from the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS) [17]. It is a Japanese case-mix classification system in which provider reimbursement is calculated per diem based on diagnostic groups. In 2015, 1262 acute care hospitals and around 580,000 beds were included in the DPC system, which encompasses more than 50% of all the hospital beds in Japan [17]. The DPC database includes comprehensive information on therapeutic procedures and patient-level data such as age, sex, diagnosis, and comorbidities at admission, activities of daily living (ADL), lengths of hospital stay, and discharge status, including in-hospital death. Disease names were recorded by both the International Classification of Diseases, 10th revision (ICD-10) codes and their Japanese names.

Data selection

The inclusion criteria were as follows: age upon admission ≥ 18 years; diagnosis of AML or MDS (ICD-10 codes: C92.0, C92.4, C92.5, C93.0, C94.0, C95.2, D462, and D469) upon admission; anticancer drugs prescribed on at least 1 day during hospitalization; calculation of medical act codes for aseptic management initiated within 7 days from the first day of chemotherapy; and prescription of either oral FLCZ, ITCZ, or VRCZ started within 7 days after the first day of chemotherapy and continued for three consecutive days or longer. The exclusion criteria were as follows: two or more antifungal drugs were prescribed in combination from the first day of admission; medical act codes for HSCT were calculated; disease name that triggered hospitalization was 'infection' (ICD-10 codes: B35-49 and J10-18); length of hospital stay was shorter than 14 days; and chemotherapy was not initiated within 28 days from admission.

Primary exposure of interest

The primary exposure of interest was the initiation of the prescription of oral VRCZ or first-generation azoles (FLCZ or ITCZ) within 7 days after chemotherapy onset. The VRCZ group and first-generation group comprised patients who filled their prescription of oral VRCZ and first-generation azole (FLCZ or ITCZ), respectively, between the first and seventh days of chemotherapy and continued treatment for three consecutive days or longer.

Outcomes

The primary outcome of this study was the proportion of patients who switched to intravenous antifungal agents within 30 days after the onset of chemotherapy following the prescription of oral VRCZ/first-generation azoles. The secondary outcomes were the length of hospital stay, defined as the total number of hospitalization days, and in-hospital mortality, defined as the proportion of all in-hospital deaths.

Covariate definition

Factors considered clinically important for the outbreak of IFIs were used as covariates. Age, sex, disease status, comorbidities noted as high-risk factors for IFIs [1, 2], ADL on admission, information about blood transfusions, granulocyte colony-stimulating factor, anticancer drugs, catheterization, and number of days from admission to the first day of chemotherapy were all included (see Electronic Supplementary Material 1).

Statistical analyses

Descriptive analyses were conducted based on the baseline characteristics of the patients in the VRCZ and first-generation groups. Continuous variables were shown as median [interquartile range (IQR)], and categorical variables as numbers with percentages (%). A Wilcoxon rank-sum test was used to compare continuous variables, and Pearson's Chi-squared test was used for between-group comparisons of categorical or binary variables. To address both measured and unmeasured confounding of the observational data, analysis using the instrumental variable (IV) method [18–22] was conducted based on two-stage least squares (2SLS) estimation [18]. The DPC database includes repeat data on patients who were hospitalized several times. Therefore, data were analyzed as "panel data," in which the observational data were pooled as a cross-section over several time-periods to deal with not only time-variant factors of repeated data, but also time-invariant factors related to the characteristics of individuals [18, 21, 23]. Analyzed as panel data, the number of individual patients was set as a panel variable, and the frequency of hospitalization was set as a time variable. A random effect model was chosen to investigate the influence of not only the factors that changed with time but also those that remained constant [18, 23].

Analysis with the IV method using 2SLS estimation

An institution's prescription preference for oral VRCZ may be a potential instrument in this method. The IV was defined as the proportion of patients prescribed oral VRCZ among all the hospitalized patients with AML at each hospital. In the first-stage model of 2SLS estimation, the probability of undergoing VRCZ was estimated by a linear regression model including covariates and the IV described above. To generate the IV, data from institutions in which none of the patients with AML/MDS were prescribed oral VRCZ or those from institutions with fewer than five patients with AML/MDS were excluded from the analyses for the avoidance of the unstable estimation of physician-specific prescription preferences for oral VRCZ [24, 25]. In the panel data analysis, unlike in the case of cross-sectional data analysis, F-statistic cannot be used for weak correlation testing. Therefore, we checked the correlation between the treatment factor (prescription of oral VRCZ) and IV using the coefficient in the first stage of 2SLS. In the second-stage model of 2SLS estimation, the association between oral VRCZ and primary/secondary outcomes was estimated using a linear regression model, conditional on the probability of undergoing VRCZ being estimated by the first-stage model and the same covariates. Analyses of the length of hospital stay were performed with both non-transformed and log-transformed values in case the distribution was right-skewed. Subgroup analyses were also performed for both primary and secondary outcomes in the following categories: age (<65 years or ≥ 65 years) and time to the start of the prescription of oral azoles (0–3 days/4–7 days after the initiation of chemotherapy).

Sensitivity analysis

Sensitivity analyses were performed to examine the impact of competing risks on the primary outcome. The hypothesized competing risk of the primary outcome is death before primary outcome occurrence. Then, the composite outcome combining the primary outcome with the competing risk was investigated. Data were analyzed using the same method as described above. The cluster-robust 95% confidence interval (CI) for heteroscedasticity was estimated by bootstrap sampling with 1000 replications. All statistical tests were two-sided, and a significance level of 5% was set. Items were excluded if less than 10% of data were provided. All analyses were conducted using Stata SE version 14.2 (Stata Corp, College Station, TX, USA).

Ethical considerations

This study was approved by the ethics committee of Kyoto University (Approval Number: R0135-6) and was performed in compliance with the Declaration of Helsinki 1964 and all its subsequent revisions, and the Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. All data were anonymized. The need for informed consent was waived.

Results

Study population and baseline characteristics

Figure 1 presents the flow chart of data selection. Data from a total of 107,761 inpatients from 1176 hospitals were screened. In total, 8642 patients from 417 hospitals met the selection criteria. For the generation of the IV, data from institutions in which none of the patients with

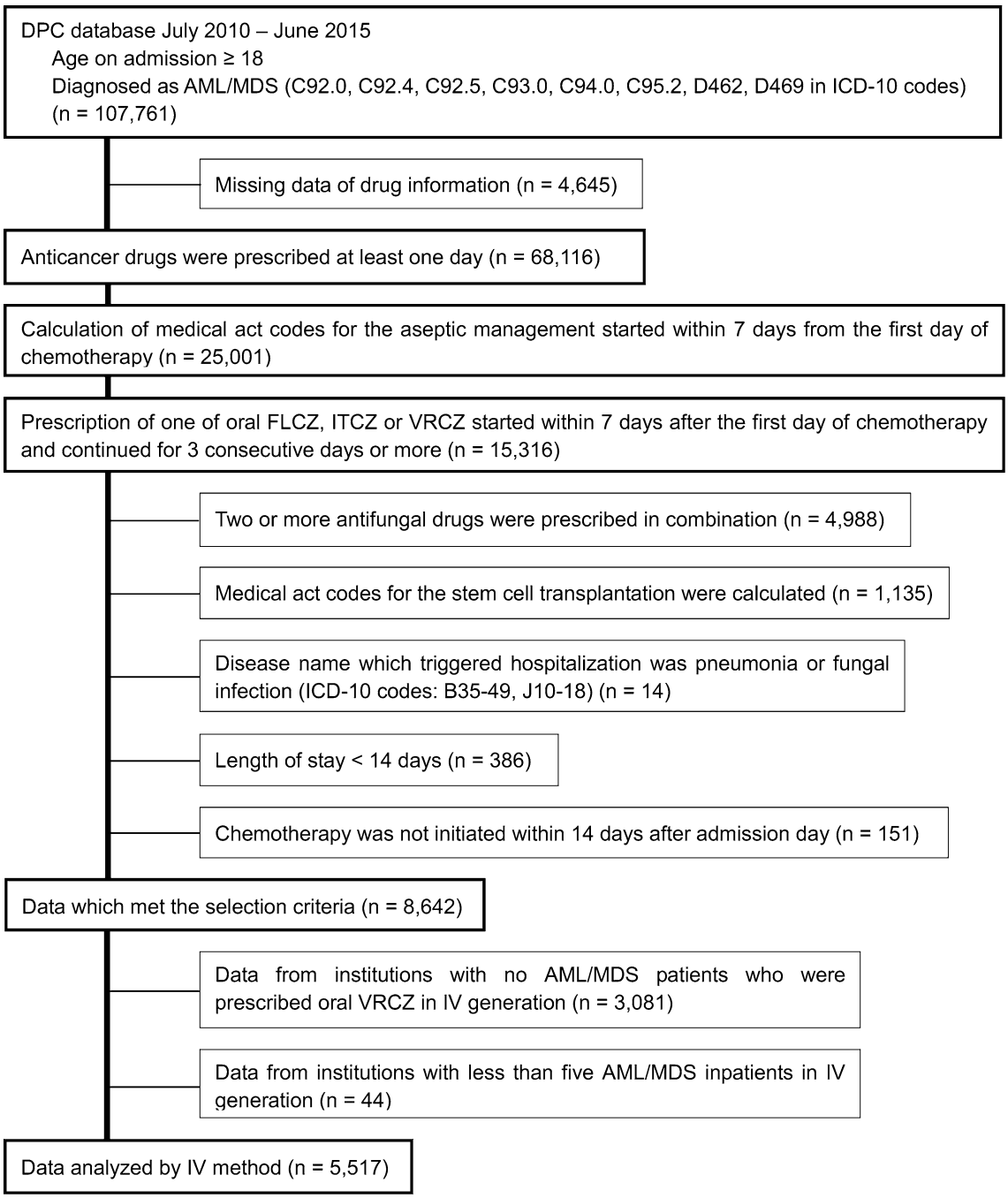

Fig. 1 Flow chart of data selection. *DPC* diagnosis procedure combination, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *ICD-10* International classification of diseases 10th revision, *FLCZ* fluconazole, *ITCZ* itraconazole, *VRCZ* voriconazole, *IV* instrumental variable

AML/MDS were prescribed oral VRCZ ($n = 3081$) and those from institutions with fewer than five patients with AML/MDS ($n = 44$) were excluded. Finally, we analyzed data from a total of 5517 patients from 142 hospitals: 471 (8.5%) were included in the VRCZ group and 5046 (91.5%) in the first-generation azole group. In the first-generation azole group, 2447 (48.5%) patients were prescribed oral FLCZ and 2599 (51.5%) were prescribed oral ITCZ. Table 1 shows the baseline characteristics of the study population analyzed with the IV method. The VRCZ group included a higher proportion of patients with recurrence (34.3% vs. 20.5%; $p < 0.001$), a greater number of elderly patients (median 64 years, IQR 51–71 years vs. median 61 years, IQR 46–69 years; $p < 0.001$), and a higher frequency of hospitalizations than the first-generation group. Overall, fungal comorbidities were more commonly observed in the

Table 1 Baseline characteristics of the study population

	Overall $n=5517$	VRCZ $n=471$	FLCZ/ITCZ $n=5046$	p value
Age, median (IQR)	62 (47–69)	64 (51–71)	61 (46–69)	< 0.001***
Sex, No (%)				
Male	3181 (57.7%)	292 (62.0%)	2889 (57.3%)	0.046*
Diagnosis at admission, No (%)				0.38
AML	5198 (94.2%)	448 (95.1%)	4750 (94.1%)	
MDS	319 (5.8%)	23 (4.9%)	296 (5.9%)	
Disease status, No (%)[a]				< 0.001***
Primary	3994 (78.3%)	278 (65.7%)	3716 (79.5%)	
Recurrence	1105 (21.7%)	145 (34.3%)	960 (20.5%)	
No. of hospitalizations, No (%)				0.040*
1	3452 (62.6%)	258 (54.8%)	3194 (63.3%)	
2	1197 (21.7%)	133 (28.2%)	1064 (21.1%)	
3	510 (9.2%)	42 (8.9%)	468 (9.3%)	
4	212 (3.8%)	22 (4.7%)	190 (3.8%)	
≥ 5	146 (2.6%)	16 (3.4%)	130 (2.6%)	
Comorbidity, No (%)				
Diabetes	649 (11.8%)	55 (11.7%)	594 (11.8%)	0.95
Kidney disease	104 (1.9%)	12 (2.5%)	92 (1.8%)	0.27
Liver disease	173 (3.1%)	22 (4.7%)	151 (3.0%)	0.046*
Heart disease	1263 (22.9%)	111 (23.6%)	1152 (22.8%)	0.72
Chronic lung disease	328 (5.9%)	19 (4.0%)	309 (6.1%)	0.067
Cerebrovascular disease	61 (1.1%)	4 (0.8%)	57 (1.1%)	0.58
Mental disorder	210 (3.8%)	16 (3.4%)	194 (3.8%)	0.63
Sepsis	292 (5.3%)	26 (5.5%)	266 (5.3%)	0.82
Pneumonia	317 (5.7%)	36 (7.6%)	281 (5.6%)	0.064
Fungal infection	576 (10.4%)	21 (4.5%)	555 (11.0%)	< 0.001***
HSCT associated	67 (1.2%)	13 (2.8%)	54 (1.1%)	0.001**
Treatment days, median (IQR)				
Red cell transfusion	2 (0–4)	2 (1–4)	2 (0–4)	0.20
Platelet transfusion	6 (3–11)	6 (3–10)	6 (3–11)	0.16
G-CSF	0 (0–4)	0 (0–4)	0 (0–3)	0.24
Anticancer drug	12 (9–17)	12 (8–17)	12 (9–17)	0.14
ADL difficulties, No (%)[b]				
Self-independent in the performance of all 10 activities	4694 (85.2%)	391 (83.2%)	4303 (85.4%)	0.20
Disability of feeding	226 (4.1%)	26 (5.5%)	200 (4.0%)	0.10
Disability of transfers	484 (8.8%)	45 (9.6%)	439 (8.7%)	0.53
Disability of grooming	249 (4.5%)	27 (5.7%)	222 (4.4%)	0.18
Disability of toilet use	356 (6.5%)	37 (7.9%)	319 (6.3%)	0.19
Disability of bathing	490 (8.9%)	54 (11.5%)	436 (8.7%)	0.039*
Disability of mobility on level surfaces	500 (9.1%)	49 (10.4%)	451 (9.0%)	0.29
Disability of stairs	649 (11.8%)	67 (14.3%)	582 (11.5%)	0.082
Disability of dressing	400 (7.3%)	43 (9.1%)	357 (7.1%)	0.099
Disability of bowels	214 (3.9%)	25 (5.3%)	189 (3.8%)	0.092
Disability of bladder	217 (3.9%)	24 (5.1%)	193 (3.8%)	0.17
Central venous catheter, No (%)	4055 (73.5%)	353 (74.9%)	3702 (73.4%)	0.46
No. of days from admission to the first day of chemotherapy, median (IQR)	3 (2–4)	2 (2–4)	3 (2–4)	0.005**
Timing to the start of the prescription of oral azoles, median (IQR)				< 0.001***
0–3 days	4578 (83.0%)	365 (77.5%)	4213 (83.5%)	
4–7 days	939 (17.0%)	106 (22.5%)	833 (16.5%)	

Table 1 (continued)

	Overall $n=5517$	VRCZ $n=471$	FLCZ/ITCZ $n=5046$	p value
Switching to intravenous antifungal agent, No (%)	1617 (29.3%)	97 (20.6%)	1520 (30.1%)	< 0.001***
Length of hospital stay, days, median (IQR)	35 (29–48)	35 (28–47)	35 (29–48)	0.080
In-hospital mortality, No (%)	309 (5.6%)	46 (9.8%)	263 (5.2%)	< 0.001***

VRCZ voriconazole, *SCT* stem cell transplantation, *G-CSF* granulocyte colony-stimulating factor, *ADL* activities of daily living, *IQR* interquartile range, *FLCZ* fluconazole, *ITCZ* itraconazole, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome

*p value < 0.05; **p value < 0.01; ***p value < 0.001

[a]418 of 5517 inpatient data were missing; [b]8 of 5517 inpatient data were missing

first-generation azole group than in the VRCZ group; however, most of these comorbidities were oral and gastrointestinal/anal candidiasis; pulmonary candidiasis or pulmonary aspergillosis was more frequently observed in the VRCZ group (Table 2).

Association between oral VRCZ prescription and reduction in the proportion of patients switched to intravenous antifungal agents

As shown in Fig. 2, a lower proportion of patients switched to intravenous antifungal agents in the VRCZ group than the first-generation azole group. The results of the analysis with the IV method showed that the proportion of patients who switched to intravenous antifungal agents was significantly reduced by 21.0% in the VRCZ group compared to that in the first-generation azole group (95% CI − 33.4 to − 8.6; $p=0.001$). Analysis by age subgroup showed that the effect size was larger in the younger population aged < 65 years (− 40.6%, 95% CI − 63.2 to − 17.9; $p<0.001$) than in older patients aged ≥ 65 years (− 21.9%, 95% CI − 35.8 to − 8.1; $p=0.002$). The results of the subgroup analysis also showed that the proportion of patients who started oral azoles within 3 days from the first day of chemotherapy was significantly lower (32.9%, 95% CI − 46.7 to − 19.2; $p<0.001$). In contrast, among patients who began oral azole treatment between the fourth and seventh days of chemotherapy, the proportion was not significantly reduced in the VRCZ group (− 9.0%, 95% CI − 33.7 to 15.7; $p=0.48$). The sensitivity analysis, which used composite outcomes to examine the impact of competing risk, confirmed these results.

We conducted additional analyses in which the first-generation azole group was divided into FLCZ and ITCZ groups (see Electronic Supplementary Material 2). Compared to the FLCZ group, the proportion of patients switched to intravenous antifungal agents was

Table 2 Characteristics of fungal comorbidities on admission

	Total $n=576$	VRCZ $n=21$	FLCZ/ITCZ $n=555$	p value
Tinea (ICD-10 code), No (%)				0.93
Tinea unguium (B351)	2 (0.3%)	0 (0.0%)	2 (0.4%)	
Tinea pedis (B353)	5 (0.9%)	0 (0.0%)	5 (0.9%)	
Tinea universalis; profunda (B358)	18 (3.1%)	1 (4.8%)	17 (3.1%)	
Candida (ICD-10 code), No (%)				0.048*
Oral (B370)	266 (46.2%)	7 (33.3%)	259 (46.7%)	
Pulmonary; allergic bronchopulmonary (B371)	14 (2.4%)	2 (9.5%)	12 (2.2%)	
Cutaneous; perineal; nail (B372)	2 (0.3%)	0 (0.0%)	2 (0.4%)	
Gastrointestinal; anal (B378)	203 (35.2%)	5 (23.8%)	198 (35.7%)	
Other candidiasis (B375-377 and 379)	49 (8.5%)	3 (14.3%)	46 (8.3%)	
Aspergillus (ICD-10 code), No (%)				< 0.001***
Invasive pulmonary aspergillosis (B440)	12 (2.1%)	3 (14.3%)	9 (1.6%)	
Pulmonary aspergillosis/aspergilloma (B441)	6 (1.0%)	1 (4.8%)	5 (0.9%)	
Other mycosis (ICD-10 code B487, B488, B49), No (%)	34 (5.9%)	3 (14.3%)	31 (5.6%)	0.097

ICD International Classification of Diseases, *VRCZ* voriconazole, *FLCZ* fluconazole, *ITCZ* itraconazole

*p value < 0.05; **p value < 0.01; ***p value < 0.001

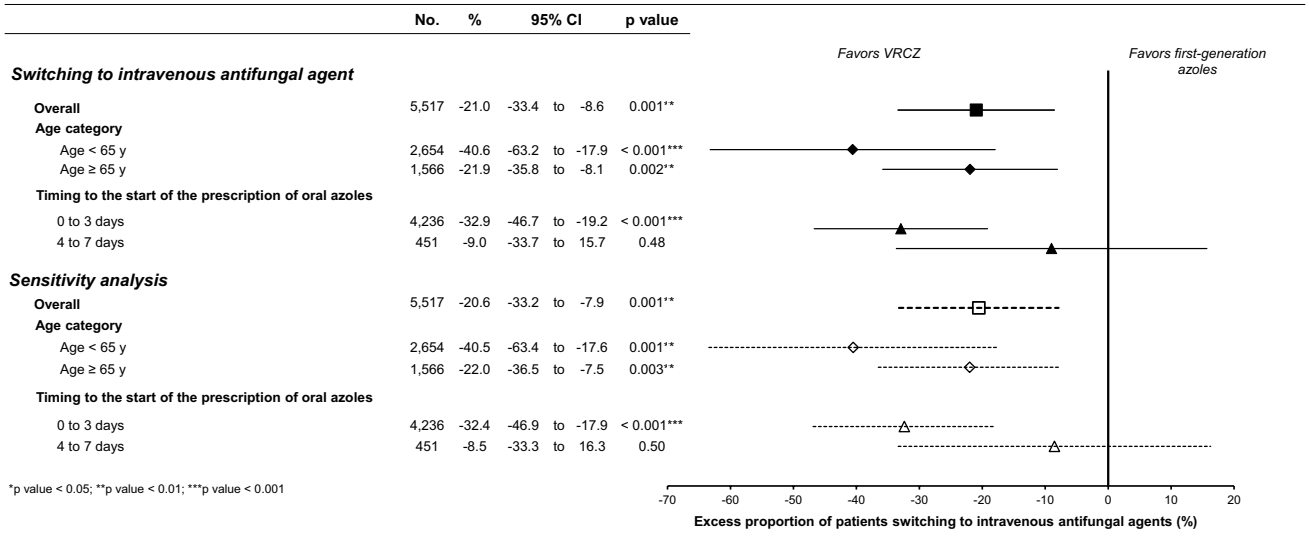

Fig. 2 Impact of administration of prescribed oral VRCZ on the proportion of patients switching to intravenous antifungal agents compared to first-generation azole administration. *VRCZ* voriconazole, *CI* confidence interval

significantly reduced by 34.4% in the VRCZ group (95% CI − 44.7 to − 24.2; $p < 0.001$). On the other hand, there was no significant difference between the VRCZ and ITCZ groups (1.21%, 95% CI − 10.4 to 12.8; $p = 0.84$).

Association between oral VRCZ prescription and length of hospital stay

Figure 3 shows the impact of oral VRCZ prescription on the length of hospital stay compared to that of first-generation azole prescription. Oral VRCZ prescription was not significantly associated with a shorter length of hospital stay compared to oral first-generation azole prescription (− 1.16 days,

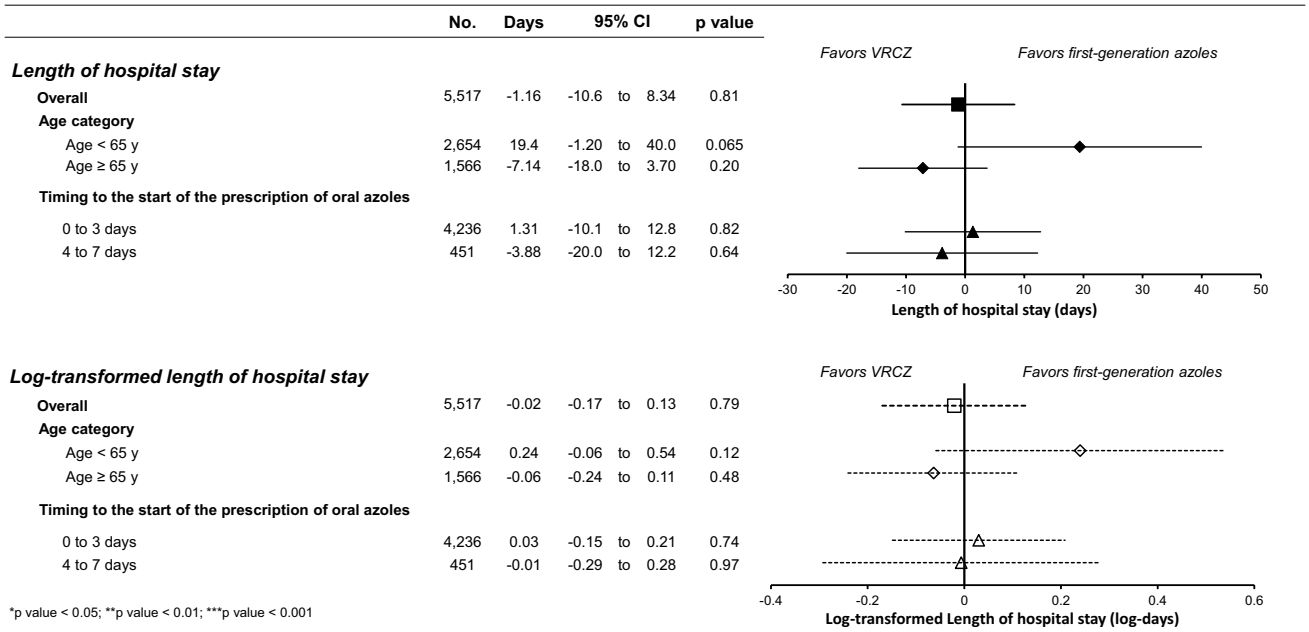

Fig. 3 Impact of administration of prescribed oral VRCZ on length of hospital stay compared to first-generation azole administration. *VRCZ* voriconazole, *CI* confidence interval

95% CI − 10.6 to 8.34; $p = 0.81$). Log transformation data analysis confirmed these results (− 0.02 log-days, 95% CI − 0.17 to 0.13; $p = 0.79$). The results of the subgroup analyses also did not show a significant association. There was no significant difference between the VRCZ group and both FLCZ and ITCZ groups (Electronic Supplementary Material 2).

Association between oral VRCZ prescription and in-hospital mortality reductions

Figure 4 shows the impact of oral VRCZ prescription on in-hospital mortality compared to that of first-generation azole prescription. The prescription of oral VRCZ was not significantly associated with a reduction in in-hospital mortality compared to that of oral first-generation azoles (− 0.7%, 95% CI − 9.4 to 8.0; $p = 0.87$). The results of the subgroup analyses also did not show a significant association. There was no significant difference between the VRCZ group and both FLCZ and ITCZ groups (Electronic Supplementary Material 2).

Discussion

The results of our study showed that oral VRCZ prescription initiated within 7 days after chemotherapy onset was significantly associated with a reduction in the use of intravenous antifungal agents compared to first-generation azoles. We also found that there was a significant association between oral VRCZ prescription and reductions in the number of patients who switched to intravenous antifungal agents, among those who started oral azole treatment within 3 days from the onset of chemotherapy, but not in those in whom it was started later. The impact of oral VRCZ on the reduction in the proportion of patients who switched to intravenous antifungal agents was stronger in patients aged < 65 years.

There are two possible situations in which reductions in the proportion of switching from oral azoles to intravenous antifungal agents occur. The first pertains to a decline in the necessity for empiric or therapeutic intravenous antifungal therapy owing to decreases in the number of events with suspicions of IFIs, while the second is related to the need to switch to intravenous antifungal agents due to the discontinuation of oral azole use owing to side effects or the condition of patients. However, previous studies have reported that the adverse events which presented following the prophylactic use of oral VRCZ were tolerable and similar to those associated with first-generation azole use [26–28]. Therefore, it is suggested that reducing switching to intravenous antifungal agents was more likely to be caused by the reduction in the occurrence of events suspected of IFI than by intolerable toxicity of antifungal prophylaxis. A single-center retrospective analysis reported that the administration of oral VRCZ before or from the onset of cytoreductive chemotherapy significantly reduced the frequency of empiric or therapeutic antifungal therapy use compared to the administration of oral FLCZ and ITCZ [26, 29]. A meta-analysis showed that a significantly smaller number of patients received empiric antifungal treatment following the prophylactic administration of oral/intravenous second-generation azoles than those receiving first-generation azoles in a population of patients with hematological disease [27]. The results of our study are in alignment with those of previous studies. In contrast, a randomized control trial reported that the prophylactic use of intravenous VRCZ was not associated with reductions in the occurrence proportions of proven/probable IFI or proportions of empirical antifungal therapy use compared to intravenous ITCZ; this may be attributed to a lack of sufficient statistical power for the estimation of significant differences [30]. The present study was conducted using a large national database and had sufficient statistical power.

Although a previous study investigated the differences in the preventive effects of VRCZ between adults and children [28], the impact of age in adult patients has not been

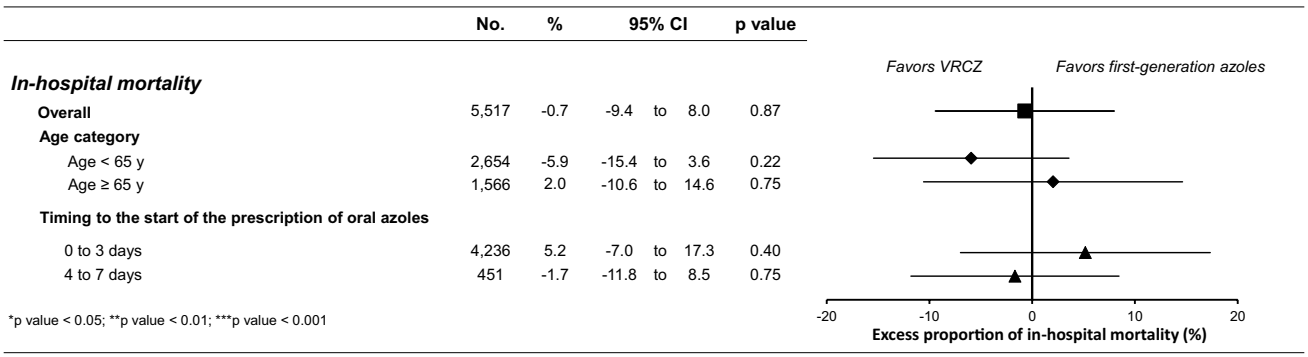

Fig. 4 Impact of administration of prescribed oral VRCZ on in-hospital mortality compared to first-generation azole administration. *VRCZ* voriconazole, *CI* confidence interval

clarified. The presented data indicated a stronger impact on the association between oral VRCZ prescription and reductions in the proportions of switching to intravenous antifungal agents in patients aged < 65 years than in older patients. It may be difficult to show more favorable results in elderly patients than younger patients, as the older patients in our study received lower intensive chemotherapy, showed greater rates of death owing to AML, or showed a greater number of complications other than those caused by IFIs compared to the younger patients. In additional analyses, the proportion of patients who switched to intravenous antifungal agents was significantly reduced in the VRCZ group compared to the FLCZ group, although it was not significantly reduced compared to the ITCZ group. The reason for this finding may be that ITCZ has favorable sensitivity to filamentous fungi and a broader spectrum than FLCZ.

In the present analysis, no significant difference was observed between oral VRCZ and first-generation azole use in terms of the length of hospital stay and in-hospital mortality, similar to previous reports [11, 16, 27, 28]. The length of hospital stay and mortality may be affected by the treatment choice after the occurrence of IFIs and/or the clinical course of AML/MDS rather than the efficacy of oral azoles.

This study is the first to verify the benefits of the early administration of oral VRCZ in patients with AML/MDS undergoing chemotherapy in a nationwide large-scale cohort. The results of this study are also novel, in that they show the impact of patient age and the appropriate timing for the initiation of oral VRCZ administration in reducing the use of intravenous antifungal agents compared to first-generation azole administration.

The present study has some limitations. First, observational studies on healthcare services face potentially "unmeasured confounding" issues [31]. Regression or propensity score methods can deal with bias from measured confounders but cannot adjust for unmeasured confounders [22]. We used the IV method to address bias from unobserved confounders and also included clinically important factors as covariates in the model to address bias from observed confounders. Second, the effects of posaconazole or other new-generation azoles could not be investigated because they have not been released yet in Japan.

In conclusion, the administration of oral VRCZ soon after intensive chemotherapy onset could benefit adult patients with AML/MDS. FLCZ followed by ITCZ is the most commonly used prophylactic regimen during chemotherapy for acute leukemia; VRCZ is rarely administered [32].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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