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ORIGINAL RESEARCH

Plasma Concentrations of Prophylactic Posaconazole and Risk Factors for Subtherapeutic Exposure in Taiwanese Patients with Hematologic Malignancies

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Background: Posaconazole is widely used for antifungal prophylaxis in patients with hematologic malignancies. However, inter-individual pharmacokinetic variability may lead to subtherapeutic exposure and treatment failure. Real-world data on the pharmacokinetics of posaconazole tablets and infusion in East Asian populations remain limited. This study aims to evaluate the plasma concentration of posaconazole and risk factors for subtherapeutic exposure in Taiwanese patients.

Methods: This nested case-control study was conducted using data from the National Taiwan University Hospital database. The study cohort comprised adult patients with hematologic malignancies receiving delayed-release tablets or intravenous formulations of posaconazole and undergoing therapeutic drug monitoring. Factors associated with subtherapeutic posaconazole exposure (<0.7 μg/mL) were identified through multivariate logistic regression. Supratherapeutic concentration was defined as a level >1.83 μg/mL.

Results: Of a total of 221 patients, 24.9% and 24.0% exhibited subtherapeutic and supratherapeutic posaconazole concentrations, respectively. Multivariate logistic regression indicated that male sex (odds ratio [OR] = 2.31), diarrhea (OR = 2.18), and concurrent use of proton pump inhibitors (OR = 2.00) or prokinetic agents (OR = 2.17) were independently associated with subtherapeutic exposure to posaconazole.

Conclusion: Subtherapeutic and supratherapeutic exposures to posaconazole remain a concern despite standard dosing. Therapeutic drug monitoring and personalized risk assessment are essential for optimizing antifungal prophylaxis in patients with hematologic malignancies.

Keywords: posaconazole, therapeutic drug monitoring, antifungal prophylaxis, hematologic malignancies

Introduction

Posaconazole is a broad-spectrum triazole antifungal agent that is widely used for the prophylaxis and treatment of invasive fungal infections (IFIs), particularly in immunocompromised patients, such as those with hematologic malignancies and those undergoing hematopoietic stem cell transplantation.[1] Evidence suggests that posaconazole effectively treats infections caused by mold species, such as *Aspergillus* and *Mucor*, by inhibiting the synthesis of ergosterol—a key component of fungal cell membranes.[2] Despite the efficacy of posaconazole, its pharmacokinetics exhibits interindividual variability, attributable to factors such as drug formulation, concomitant medication use, albumin level, body weight, gastrointestinal function, and genetic polymorphisms in drug-metabolizing enzymes.[3–6] This variability may lead to subtherapeutic or supratherapeutic drug concentrations in plasma, influencing treatment success and safety.[7] Higher plasma concentrations of posaconazole have been associated with more favorable clinical outcomes.[8] Therefore,

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researchers have recommended therapeutic drug monitoring (TDM) to guide dose adjustment and ensure optimal exposure.[8,9] Current TDM guidelines recommend posaconazole trough concentrations of ≥0.7 μg/mL for prophylaxis and ≥1.0–1.25 μg/mL for treatment, with a suggested upper limit of 3.75 μg/mL.[10] However, one study reported that a concentration of >1.83 μg/mL was associated with hepatotoxicity.[11,12]

Three formulations of posaconazole are currently available for clinical use: an oral suspension, a delayed-release tablet, and an intravenous injection. The oral suspension exhibits variable and food-dependent bioavailability, and its absorption is substantially compromised by gastrointestinal disturbances, mucositis, or concomitant use of acid-suppressive agents.[13] Consequently, many patients, particularly those who are immunocompromised, fail to achieve target serum concentrations when using oral suspension.[14] By contrast, the delayed-release tablet exhibits improved and predictable absorption, given that it dissolves in the small intestine and is less influenced by gastric pH or food intake. This tablet form facilitates the attainment of therapeutic drug levels.[6,9]

A fixed-dose regimen (300 mg twice on day 1, followed by 300 mg once daily) is recommended in patients receiving the delayed-release tablet or infusion of posaconazole. However, pharmacokinetic evidence indicates that body weight is an important determinant of posaconazole exposure.[4] Several real-world studies have also identified body weight as a significant risk factor for failing to achieve target concentrations.[15,16] Because Asian populations generally have lower body weight than Western populations, the plasma concentrations distribution of posaconazole may differ substantially between these groups.

Prior studies in East Asian populations have largely examined the oral suspension, were limited by small sample sizes, and rarely assessed protein-binding–related factors such as total bilirubin.[9,17,18] Moreover, most investigations have focused exclusively on subtherapeutic concentrations, with minimal characterization of supratherapeutic exposure that may have safety implications.[9,17–19] Real-world pharmacokinetic data for the delayed-release tablet and intravenous formulations in Taiwanese populations remain particularly scarce. To address these gaps, we conducted the largest real-world analysis of posaconazole plasma concentrations in Taiwanese patients with hematologic malignancies receiving antifungal prophylaxis, using both tablet and intravenous formulations. This study provides a comprehensive evaluation of the full exposure range (including both subtherapeutic and supratherapeutic levels) examines exploratory associations with breakthrough IFIs, and identifies clinically relevant factors contributing to inadequate posaconazole exposure.

Methods

Study Design and Data Source

This nested case-control study was conducted using data from the Integrated Medical Database of National Taiwan University Hospital. This database was established in 2013 to facilitate the use of extensive clinical data for medical services and research. It contains comprehensive outpatient, inpatient, and emergency department records, which are accessible to authorized researchers for investigative and academic purposes.[20] The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 202208071RINA). Because the data were deidentified, no informed consent was required. This study was conducted in accordance with the Declaration of Helsinki.

Study Cohort and Selection Criteria

This study included individuals aged ≥18 years who received a diagnosis of a hematologic malignancy between July 1, 2016, and December 31, 2020. Hematologic malignancies were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes. Patients with acute myeloid leukemia (*ICD-10-CM* codes: C92.XX, C93.XX, C95.0X, and C95.9X), those with myelodysplastic syndromes (*ICD-10-CM* code: C94.6), and those who had undergone allogeneic hematopoietic cell transplantation (*ICD-10-CM* codes: Z94.81 and Z94.84) were considered to have hematologic malignancies. Eligible patients were required to have received posaconazole in a delayed-release tablet or infusion for prophylaxis against IFIs during the study period. In Taiwan, posaconazole prophylaxis is reimbursed only for specific high-risk patients: those ≥13 years with grade III–IV acute graft versus

host disease requiring high-dose steroids after hematopoietic stem cell transplantation, and patients with acute myeloid leukemia or high-risk myelodysplastic syndrome undergoing high-intensive induction chemotherapy regimens.

Patients who had at least one posaconazole TDM record after the achievement of steady-state concentrations, defined as at least 5 days after the initial posaconazole dose, and those who received a standard posaconazole dose of 300 mg daily were included in this study. Patients whose first posaconazole TDM results were not recorded during hospitalization were excluded from this study.

The study cohort was divided into a case group and a control group on the basis of the plasma concentration of posaconazole. Patients with posaconazole concentrations of <0.7 μg/mL were assigned to the case group, whereas those with posaconazole concentrations of ≥0.7 μg/mL were assigned to the control group.

Covariates

Statistical models used in this study were adjusted for several potential risk factors and patient characteristics. These covariates included age, sex, body weight, body mass index, poor oral intake, diarrhea, concomitant medication use, loading dose administration, posaconazole dosage form, hepatic and renal function, C-reactive protein (CRP) level, and serum albumin level. Concomitant medications of interest included proton pump inhibitors (PPIs), H_2 receptor antagonists, prokinetic agents (metoclopramide, domperidone, and mosapride), posaconazole metabolic inducers (eg, lorazepam and rifampin), and metabolic inhibitors (eg, cobicistat). Poor oral intake was defined as being nil per os (NPO), receiving intravenous nutrition, or consuming less than 50% of daily nutritional requirements during the four days prior to the TDM measurement.

Clinical Outcomes

A breakthrough IFI is defined as an invasive fungal infection that occurs while the patient is receiving antifungal prophylaxis or treatment. Due to the limitations inherent in a retrospective study design, we adapted the definitions of possible IFI and probable IFI based on the criteria of the European Organization for Research and Treatment of Cancer's Mycoses Study Group.[21] In this study, possible IFI was defined as a switch from posaconazole to another antifungal agent occurring between 5 days after the initiation of posaconazole and 1 day after its discontinuation. Probable IFI was defined as possible IFI accompanied by positive microbiological findings, such as two consecutive serum Aspergillus antigen levels >0.5, a positive cryptococcal antigen test, or a positive fungal culture. Clinical outcomes were assessed until patient discharge. For patients whose posaconazole prophylaxis was discontinued before discharge, an additional follow-up period of two weeks after discontinuation was included.

Statistical Analysis

Patient characteristics were compared between the case and control groups to identify potential risk factors for subtherapeutic posaconazole exposure. Categorical variables are presented as number (percentage) values, whereas continuous variables are presented as median (first quartile, third quartile) values. The normality of continuous variables was assessed using the Shapiro–Wilk test. Variables that met the assumption of normal distribution were analyzed using the independent *t*-test, whereas non-normally distributed variables were evaluated using the Mann–Whitney *U*-test. The chi-square or Fisher exact test were used for the categorical variables.

To identify independent risk factors after covariate adjustment, multivariate logistic regression was performed using the backward selection method for variable inclusion. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. All variables were initially entered into a regression model, and the variable with the highest *P* value was sequentially removed. This process continued until all remaining variables had a *P* value of <0.15. Variables with a *P* value of <0.05 were considered statistically significant in the final model. Data were managed and analyzed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

We initially identified 4026 patients with hematologic malignancies. Of them, 221 patients met the eligibility criteria and were thus included in this study. The case and control groups comprised 55 and 166 patients, respectively. Figure 1 presents a flowchart depicting patient selection.

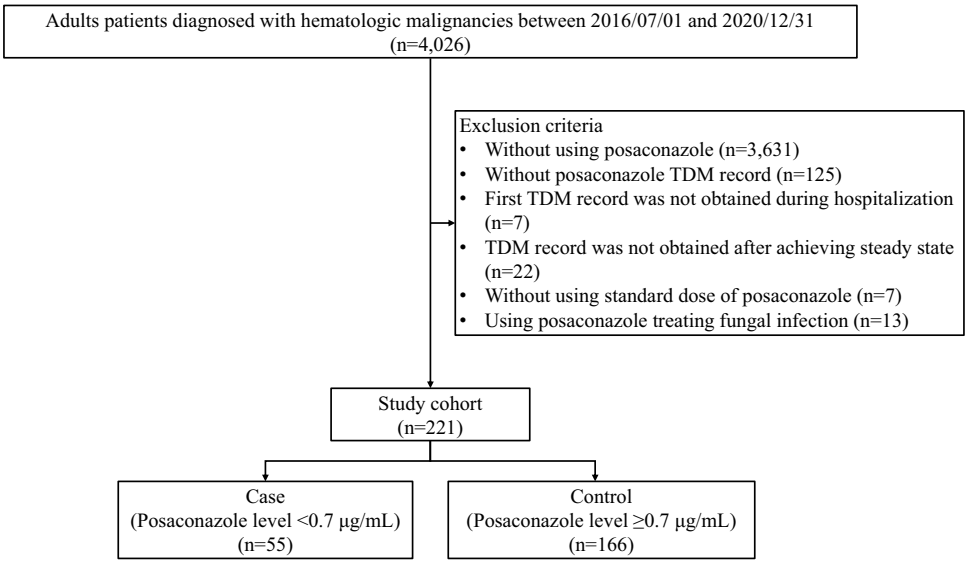

Figure 1 Flowchart depicting patient selection.

Table 1 presents the baseline characteristics of the study cohort. The proportions of patients with posaconazole concentrations of <0.7, 0.7–1.83, and >1.83 μg/mL were 24.9%, 51.1%, and 24.0%, respectively. The proportion of male patients was higher in the case group than in the control group (61.8% vs 44.6%). Furthermore, the prevalence of

Table 1 Baseline Characteristics of the Overall Study Cohort, Case and Control Groups

Characteristics	All Patients (n=221)	Posaconazole Level <0.7 μg/mL (n=55)	Posaconazole Level ≥0.7 μg/mL (n=166)	*p*-value
Median age, years (Q1, Q3)	54 (41, 64)	54 (44, 63)	54 (41, 64)	0.892
Male, n (%)	108 (48.9)	34 (61.8)	74 (44.6)	0.027
Posaconazole concentration, μg/mL				-
Mean±SD	1.30±0.76	0.51±0.12	1.57±0.70	
Median (Q1, Q3)	1.11 (0.70, 1.79)	0.52 (0.42, 0.60)	1.39 (1.03, 1.98)	
Posaconazole concentration by group, n (%)				-
<0.7 μg/mL	55 (24.9)	55 (100)	0 (0)	
0.7–1.82 μg/mL	113 (51.1)	0 (0)	113 (68.1)	
≥1.83 μg/mL	53 (24.0)	0 (0)	53 (31.9)	
Median weight, kg (Q1, Q3)	61.9 (53.6, 71.0)	60.3 (53.4, 69.7)	62.3 (53.9, 71.3)	0.917
Median BMI, kg/m^2 (Q1, Q3)	23.2 (21.2, 25.5)	22.7 (20.6, 25.1)	23.4 (21.4, 25.6)	0.273
ALT ≥120 U/L, n (%)[a]	9 (4.1)	2 (3.6)	7 (4.2)	1.000
T-Bil ≥1.2 mg/dL, n (%)[b]	43 (19.5)	15 (27.3)	28 (16.9)	0.091
Median eGFR, mL/min/1.73 m^2 (Q1, Q3)[c]	119.1 (95.3, 144.9)	126.9 (105.0, 146.1)	115.9 (92.7, 144.5)	0.773
Albumin <3.5 g/dL, n (%)[d]	99 (44.8)	30 (54.6)	69 (41.6)	0.093
Median CRP (Q1, Q3)[e]	3.20 (1.48, 7.50)	2.47 (0.97, 4.56)	3.61 (1.65, 8.59)	0.070*
With loading dose, n (%)	77 (34.8)	18 (32.7)	59 (35.5)	0.704
Intravenous posaconazole use, n (%)	11 (5.0)	4 (7.3)	7 (4.2)	0.473
Poor intake, n (%)	63 (28.5)	19 (34.6)	44 (26.5)	0.252
Diarrhea, n (%)	52 (23.5)	17 (30.9)	35 (21.1)	0.137
Proton pump inhibitors use, n (%)	113 (51.1)	33 (60.0)	80 (48.2)	0.129
H_2-receptor antagonists use, n (%)	51 (23.1)	11 (20.0)	40 (24.1)	0.532
Prokinetics use, n (%)	47 (21.3)	15 (27.3)	32 (19.3)	0.209
With metabolic inducer, n (%)[f]	32 (14.5)	4 (7.3)	28 (16.9)	0.080
With metabolic inhibitor, n (%)[g]	1 (0.5)	0 (0)	1 (0.6)	1.000

Notes: *The data was analyzed using the Mann–Whitney *U*-test. [a]There were 221 patients with ALT data before therapeutic drug monitoring (TDM). [b]There were 220 patients with T-Bil data before TDM. [c]There were 221 patients with eGFR data before TDM. [d]There were 187 patients with albumin data before TDM. [e]There were 192 patients with CRP data before TDM. [f]Posaconazole metabolism inducer included lorazepam and rifampin. [g]Posaconazole metabolism inhibitor included cobicistat.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NA, not applicable; Q1, first quartile; Q3, third quartile; T-Bil, total bilirubin.

Table 2 Risk Factors for Subtherapeutic Posaconazole Concentrations

Risk Factors	Posaconazole Level <0.7 μg/mL (n=55)	Posaconazole Level ≥0.7 μg/mL (n=166)	*p*-value	Multivariable Logistic Regression	
				OR (95% CI)	*p*-value
Male, n (%)	34 (61.8)	74 (44.6)	0.027	2.31 (1.17–4.56)	0.016*
Median age, years (Q1, Q3)	54 (44, 63)	54 (41, 64)	0.892		
Median BMI, kg/m^2 (Q1, Q3)	22.7 (20.6, 25.2)	23.4 (21.4, 25.6)	0.273		
Median CRP (Q1, Q3)	2.47 (0.97, 4.56)	3.61 (1.65, 8.59)	0.070#	0.95 (0.90–1.00)	0.069
ALT ≥120 U/L, n (%)	2 (3.6)	7 (4.2)	1.000		
T-Bil ≥1.2 mg/dL, n (%)	15 (27.3)	28 (16.9)	0.091	2.16 (0.97–4.78)	0.058
Albumin <3.5 g/dL, n (%)	30 (54.6)	69 (41.6)	0.093		
With loading dose, n (%)	18 (32.7)	59 (35.5)	0.704		
Poor intake, n (%)	19 (34.6)	44 (26.5)	0.252		
Diarrhea, n (%)	17 (30.9)	35 (21.1)	0.137	2.18 (1.04–4.54)	0.038*
Proton pump inhibitors use, n (%)	33 (60.0)	80 (48.2)	0.129	2.00 (1.01–4.66)	0.049*
H_2-receptor antagonists use, n (%)	11 (20.0)	40 (24.1)	0.532		
Prokinetics use, n (%)	15 (27.3)	32 (19.3)	0.209	2.17 (1.01–4.66)	0.048*

Notes: # The data was analyzed using the Mann–Whitney *U*-test, * $p < 0.05$.
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; OR, odds ratio; Q1, first quartile; Q3, third quartile; T-Bil, total bilirubin.

Table 3 Rates of Breakthrough IFIs and Mortality in the Case and Control Groups

Results	Posaconazole Level <0.7 μg/mL (n=55)	Posaconazole Level ≥0.7 μg/mL (n=166)
All breakthrough IFI, n (%)	17 (30.9)	34 (20.5)
Possible IFI, n (%)	11 (20.0)	23 (13.9)
Probable IFI, n (%)	6 (10.9)	11 (6.6)
In-hospital mortality, n (%)	6 (10.9)	12 (7.2)

Abbreviation: IFI, invasive fungal infection.

hyperbilirubinemia, hypoalbuminemia, diarrhea, poor oral intake, and concomitant PPI or prokinetic agent use was higher in the case group than in the control group. By contrast, the level of CRP was higher in the control group than in the case group (3.61 vs 2.47 mg/dL).

Table 2 presents the results of the univariate and multivariate analyses. In the univariate analysis, most potential risk factors were not significantly associated with subtherapeutic posaconazole exposure, except for male sex. After all candidate variables were included and backward selection was performed, the multivariate model retained six variables. Among these variables, male sex (OR = 2.31, 95% CI = 1.17–4.56), diarrhea (OR = 2.18, 95% CI = 1.04–4.54), PPI use (OR = 2.00, 95% CI = 1.01–4.66), and prokinetic agent use (OR = 2.17, 95% CI = 1.01–4.66) were significantly associated with an increased risk of subtherapeutic posaconazole exposure. In the analysis of fungal infection, the case group showed numerically higher rates of breakthrough invasive fungal infections (30.9% vs 20.5%) and in-hospital mortality (10.9% vs 7.2%) compared with the control group. (Table 3).

Discussion

In this study, we explored the real-world plasma concentrations of posaconazole in Taiwanese patients with hematologic malignancies receiving antifungal prophylaxis. We further identified key risk factors for subtherapeutic posaconazole exposure. Of the included patients, 24.9% failed to achieve the recommended prophylactic trough concentration of ≥0.7 μg/mL despite receiving a standard posaconazole dosage in a delayed-release tablet or intravenous injection form. Notably, male sex, diarrhea, and concomitant PPI or prokinetic agent use were independently associated with an

increased risk of subtherapeutic posaconazole exposure. In addition, hyperbilirubinemia was associated with a trend toward reduced drug exposure, and biomarkers of inflammation tended to correlate with increased concentrations, although the between-group differences were nonsignificant.

The multivariate analysis indicated male sex, diarrhea, and concomitant PPI or prokinetic agent use as significant risk factors for subtherapeutic posaconazole exposure. This finding is consistent with those of studies indicating that PPI use increases the risk of subtherapeutic posaconazole exposure, likely by altering gastrointestinal pH, which in turn impairs the solubility and absorption of posaconazole, even in its delayed-release form.[18,22] Although the tablet form of posaconazole was developed to address pH-dependent absorption problems, impaired absorption is observed with PPI use in certain patients, necessitating continued TDM. In the present study, diarrhea and concomitant use of prokinetic agents such as metoclopramide were significantly associated with reduced drug exposure. Bui et al[23] reported that both diarrhea and regular metoclopramide use were significantly associated with subtherapeutic concentrations of posaconazole in the tablet form. The mechanism by which diarrhea affects absorption is likely related to reduced gastrointestinal transit time, which leads to inadequate drug dissolution and intestinal uptake.[23] Prokinetic agents may accelerate gastric emptying and intestinal motility, thereby reducing the duration of posaconazole exposure to absorptive surfaces in the small intestine.[24] These findings collectively highlight the need for caution and close monitoring in patients with gastrointestinal dysfunction and in those on medications affecting intestinal motility. In our cohort, male sex was identified as another independent risk factor for subtherapeutic posaconazole concentration. A study reported that male patients were more likely than female patients to exhibit low posaconazole concentrations.[23] Our finding may be attributable to sex-based differences in body composition, particularly higher body weight in male individuals than in female individuals (69.0 vs 55.5 kg, $p<0.001$, Supplemental Table 1), which may result in a larger distribution volume and lower plasma concentrations in men than in women. Although posaconazole is a highly lipophilic drug, higher body weight in males does not necessarily reflect greater adiposity; it may instead be attributed to increased muscle and bone mass. Previous studies have also demonstrated an association between male sex and subtherapeutic posaconazole concentrations even after adjustment for body weight, suggesting that factors beyond body mass such as hepatic metabolism or gastric transit time may contribute to these differences.[22,23]

Our findings indicated that hypoalbuminemia and hyperbilirubinemia influenced posaconazole exposure. Posaconazole is a highly protein-bound antifungal agent (>98%) whose total plasma concentration is strongly determined by the serum level of albumin.[2] In patients with hypoalbuminemia, total drug concentrations may appear deceptively low, although the pharmacologically active unbound fraction remains within the therapeutic range. Evidence suggests that relying exclusively on total concentrations for TDM can lead to inappropriate dose escalation and increased toxicity in patients with hypoalbuminemia.[25] Therefore, total concentrations must be corrected using albumin-adjusted formulas (eg, $C_{adj} = C_{total} \times 4.4/Alb$), similar to phenytoin correction.[25] Elevated total bilirubin level may also alter protein binding by posaconazole. Bilirubin competes with posaconazole for the binding sites on albumin, potentially displacing the drug and increasing its unbound fraction.[26] As in hypoalbuminemia, this increase in free drug concentration corresponds to a reduction in the measured total drug concentration, leading to the misinterpretation of subtherapeutic exposure. Moreover, because the unbound fraction is available for hepatic metabolism, the displacement may accelerate drug clearance, further reducing the total concentration. Overall, these dynamics underscore a key limitation of conventional total-level TDM and highlight the need for unbound posaconazole monitoring, particularly in patients with hepatic dysfunction or altered protein-binding profiles.

Our findings emphasize the clinical implications of subtherapeutic and supratherapeutic concentrations of posaconazole. In our cohort, approximately 25% of the patients exhibited subtherapeutic posaconazole concentrations, consistent with the findings of a real-world study, where many patients failed to achieve target exposure despite receiving the tablet form of posaconazole.[27] Although baseline characteristics were not adjusted, the case group exhibited numerically higher rates of breakthrough IFIs and in-hospital mortality than did the control group, consistent with the findings of studies associating lower posaconazole concentrations with higher fungal infection risks.[8,9] In the present study, high concentrations of posaconazole were observed in the cohort, with approximately 25% of the patients having concentrations exceeding 1.83 μg/mL, a threshold previously associated with an increased risk of hepatotoxicity.[11] Although the current consensus indicates a posaconazole upper limit of 3.75 μg/mL, hepatotoxicity has been reported at lower thresholds in

populations with hematologic malignancies, emphasizing the need to consider personalized risk assessment and avoid exclusive reliance on fixed cutoffs.[10]

We investigated the effect of systemic inflammation on the pharmacokinetics of posaconazole. Inflammatory states, commonly reflected by elevated CRP levels, suppress the expression and activity of hepatic drug-metabolizing enzymes and transporters, particularly cytochrome P450 enzymes such as CYP3A4.[28] This inflammation-mediated downregulation has been extensively documented in the context of voriconazole, where it contributes to elevated plasma levels and increased toxicity under inflammatory conditions.[29] Although posaconazole is structurally similar to voriconazole, the drugs differ substantially in terms of metabolism. Posaconazole undergoes minimal CYP-mediated metabolism and is primarily eliminated through glucuronidation by UGT enzymes, particularly UGT1A4.[2] Systemic inflammation downregulates the expression and activity of UGT enzymes; consequently, glucuronidation-based metabolism is compromised.[28] However, in our cohort, no significant correlation was noted between CRP level and the total posaconazole concentration. This finding may be attributable to the relatively small contribution of hepatic metabolism to the overall clearance of posaconazole, given that the drug is largely excreted without any change through the fecal route. Consistent with our study, a prospective study by Märtson et al[30] revealed no significant association between CRP level and posaconazole trough concentration, confirming that systemic inflammation exerts a negligible effect on the pharmacokinetics of posaconazole. Together, the findings suggest that inflammation does not substantially affect the disposition of posaconazole in most clinical settings.

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of our findings to broader populations or different clinical settings. Second, only total plasma concentrations of posaconazole were measured, without corresponding free drug concentrations. Because posaconazole is a highly protein-bound agent, the total concentration may not fully reflect the pharmacologically active fraction of this drug, particularly in patients with hypoalbuminemia or hyperbilirubinemia, which can alter drug-protein binding and may lead to TDM misinterpretation. Third, although numerical differences were observed in clinical outcomes such as breakthrough IFIs and in-hospital mortality, the definitions of possible and probable IFI in our study differed from the EORTC/MSG criteria due to data limitations. These findings were not adjusted for baseline characteristics and should therefore be interpreted with caution and considered exploratory. Finally, we did not consider the presence of genetic polymorphisms or the activity of hepatic enzyme—factors that may influence the metabolism and disposition of posaconazole. Future studies should incorporate pharmacogenomic and free drug concentration monitoring to offer comprehensive insights into interindividual variability in posaconazole pharmacokinetics.

Conclusion

Many Taiwanese patients with hematologic malignancies do not achieve the target concentration of posaconazole despite standard dosing. Our findings suggest that male sex, diarrhea, and concomitant PPI and prokinetic agent use are associated with an increased risk of subtherapeutic posaconazole exposure. Furthermore, inflammation appears to have a minimal effect on posaconazole concentration. Both subtherapeutic and supratherapeutic concentrations of posaconazole are common. Notably, patients with subtherapeutic exposure exhibited numerically higher rates of breakthrough invasive fungal infections compared with those who achieved adequate concentrations, although these exploratory findings were not adjusted for baseline differences. Collectively, these observations highlight the importance of individualized dose optimization and close monitoring to ensure adequate prophylactic coverage in this high-risk population.

Data Sharing Statement

The data used and analyzed in this study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital (approval number: 202208071RINA). Given the retrospective nature of this study, the requirement for informed consent was

waived. All patient identifiers were removed before analysis. This study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no competing interests.

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