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Safety and Effectiveness of Isavuconazole Treatment for Invasive Fungal Infections in Chinese Patients with Haematologic Diseases: A Case Series

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Objective: Isavuconazole (ISZ), a newer antifungal agent approved for treating invasive aspergillosis and mucormycosis, has been available in China since 2022. However, real-world data on ISZ use among Chinese patients with hematological diseases remain limited. In this study, we present our experience with ISZ for invasive fungal infection (IFI) management in hematology patients.

Methods: Data on patient characteristics, ISZ administration variables, IFI treatment response to ISZ, and potential ISZ-associated adverse events in hematology patients from our center were retrospectively analyzed.

Results: A total of 25 hematology patients treated with ISZ were included. One (4.0%) patient had proven IFI, 13 (52.0%) had probable IFI, and the remaining 11 (44.0%) were classified as having possible IFI. ISZ was used as primary therapy in 8 cases (32.0%) and salvage therapy in 17 cases (68.0%). The switch to ISZ as salvage therapy was driven by refractoriness to primary therapy in 70.6% of cases and by refractoriness and intolerance to prior antifungal treatment in 29.4%. Clinical improvement was observed in 16 (64.0%) patients. Five patients died during hospitalization, and four discontinued therapy due to clinical deterioration. Adverse events potentially attributable to ISZ occurred in 5 patients (20.0%), including nephrotoxicity, hepatotoxicity, and blurred vision (1 case each), and with the remaining two cases involving combined hepatorenal toxicity.

Conclusion: ISZ demonstrates promising clinical efficacy and a favorable safety profile for IFI treatment in Chinese patients with hematologic diseases.

Keywords: Isavuconazole, invasive fungal infections, hematological diseases, antifungal, Chinese patients

Introduction

Patients with hematological diseases, particularly those with prolonged neutropenia or undergoing hematopoietic stem-cell transplantation (HSCT), are at high risk of invasive fungal infections (IFIs).[1,2] Aspergillosis and candidiasis are the most common IFIs in hematologic settings, while fungi such as *Mucorales* are increasingly reported. The overall mortality rate of IFIs ranges from 28% to 52.9%, depending on host factors and etiology.[3] Given the life-threatening nature of IFIs, aggressive antifungal therapy is essential.

First-line therapies for invasive aspergillosis (IA), invasive candidiasis (IC) and IFI due to molds other than *Aspergillus*, such as invasive mucormycosis (IM), are voriconazole (VOR),[4] echinocandins,[5] and liposomal amphotericin B (LAmB).[6] However, these agents have notable limitations. VOR exhibits unpredictable, non-linear pharmacokinetics, necessitating therapeutic drug monitoring (TDM) to optimize dosing regimens. Due to extensive hepatic metabolism, VOR is prone to frequent drug–drug interactions. Adverse effects of VOR, such as nephrotoxicity and hepatotoxicity, have been widely

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reported. Moreover, the emergence of drug-resistant strains has reduced VOR's efficacy compared to earlier observations.[7] Echinocandins have a narrow antifungal spectrum, and emerging resistance poses a growing concern in clinical practice. The primary limitation of LAmB is toxicity, particularly nephrotoxicity. Both echinocandins and LAmB lack oral formulations. Isavuconazole (ISZ), a newer triazole antifungal, offers oral and intravenous formulations, a broad antifungal spectrum (encompassing common yeasts, endemic fungi, and molds, including *Mucorales*), predictable pharmacokinetics, and a favorable safety profile, positioning it as a promising alternative for IFI treatment in high-risk populations.

ISZ has been available in China since 2022. Clinical trials have confirmed that the efficacy of ISZ for treating IA and IM is comparable to that of VOR and LAmB, with a lower incidence of adverse effects.[8,9] Furthermore, ISZ demonstrates efficacy in invasive candidiasis (IC) management, albeit potentially less potent than echinocandins,[10] and serves as a step-down therapy alternative following IC stabilization.[11] ISZ is currently approved for IA and IM treatment. However, real-world evidence on ISZ use among Chinese hematology patients remains limited.

In this study, we review our experience with ISZ for treating IFI in hematologic patients, focusing on indications for ISZ initiation, clinical efficacy, and safety profile.

Methods

Study Design and Participants

This retrospective study included hematologic patients treated with ISZ at Tongji Hospital (Wuhan, China) between June 1, 2022, and May 31, 2024. Exclusion criteria comprised: (1) ISZ therapy duration <3 days; (2) age <18 years; and (3) incomplete or poor-quality clinical records. The study complies with the Declaration of Helsinki. Owing to the retrospective nature of this cohort study, informed consent was waived by the Tongji Hospital Ethics Review Committee. Information was collected anonymously from the electronic medical system, and all authors ensured confidentiality of patient data.

Procedures

Data on demographics, underlying hematologic disease-related variables, comorbidities, IFI type and site, neutropenia status at infection onset, ISZ administration-related variables along with prior antifungal prophylaxis and antifungal therapy, concurrent infections, and co-administered antimicrobials were collected. Outcome data, including therapeutic response and potential ISZ-associated adverse events, were also recorded. The study protocol was approved by the Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology.

IFI were classified as proven, probable, or possible based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) criteria.[12] To evaluate the possible adverse events of ISZ, the changes of the liver function, renal function and electrocardiogram parameters before and after ISZ administration were reviewed. Nephrotoxicity was defined as one of the following: (1) increase in serum creatinine (SCR) by ≥ 26.5 (μmol/l) within 48 hours; (2) increase in SCR ≥ 1.5 times baseline within the previous 7 days; (3) urine volume ≤0.5 mL/kg/h for 6 hours. Hepatotoxicity was defined as Hy's Law cases that alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times of the upper limit of normal (ULN) and total bilirubin (TBIL) >2 ULN. QT interval changes were defined as the corrected QT intervals (QTc) equals outside the range of 350 ms to 450 ms in men or 360 ms to 460 ms in women. Therapeutic response was assessed on day 42 post-ISZ initiation or at therapy completion if treatment lasted <42 days. Clinical improvement encompassed complete response or partial response (clinical/radiological improvement without full resolution).

Statistics

Data are presented as median (min-max) or as the number and percentage, as appropriate.

Results

Twenty-five hematology patients (12 males and 13 females) who received ISZ treatment were included in this study. The characteristics of patients are summarized in Tables 1 and S1. The median age (min-max) of the patients was 48 (20–72) years. Eight (32.0%) patients were diagnosed with acute myelocytic leukemia (AML), 4 (16.0%) patients were diffuse large B-cell

Table 1 Patient Characteristics

Case No.	Age, yr	Sex	Underlying Disease	Disease Status	Transplant/ Type	Diagnosis of IFI	Species Identified	Site of Infection	Neutropenia at the Onset of IFI
1	59	F	AML	Active	NO/NA	Probable	*Candida*	Lung	No
2	72	M	DLBCL	Remission	NO/NA	Probable	*Aspergillus; Candida*	Lung	No
3	43	F	SAA	Remission	Yes/Allogeneic	Probable	*Mucorales*	Lung; Intracalvarium	No
4	52	M	DLBCL	Active	Yes/Autologous	Possible	None	Lung	No
5	22	M	AML	Active	NO/NA	Possible	None	Lung	Yes
6	70	F	DLBCL	Active	NO/NA	Possible	None	Lung	No
7	48	F	AML	Active	Yes/Allogeneic	Probable	*Aspergillus*	Lung; Enterocoelia	Yes
8	52	F	FL	Remission	NO/NA	Possible	None	Lung	No
9	38	M	T-LBL	Remission	Yes/Allogeneic	Probable	*Aspergillus*	Lung	No
10	20	M	AMLL	Remission	Yes/Allogeneic	Probable	*Aspergillus*	Lung	No
11	66	F	DLBCL	Active	NO/NA	Possible	None	Lung	No
12	51	F	FL	Remission	Yes/Autologous	Probable	*Mucorales*	Lung; Maxillofacial region	No
13	20	M	SAA	Active	Yes/Allogeneic	Probable	*Aspergillus*	Lung; Gastrointestinal tract	Yes
14	37	F	MS	Remission	Yes/Allogeneic	Probable	*Aspergillus*	Lung	No
15	68	F	HPS	Active	NO/NA	Probable	*Aspergillus; Mucorales*	Lung	Yes
16	37	M	ANKL	Active	Yes/Allogeneic	Possible	None	Lung	No
17	47	F	AML	Active	NO/NA	Possible	None	Lung	Yes
18	59	M	ANKL	Active	NO/NA	Proven	*Aspergillus*	Lung	No
19	56	F	AML	Remission	Yes/Allogeneic	Probable	*Mucorales*	Lung	Yes
20	36	M	AML	Active	NO/NA	Possible	None	Lung	Yes
21	54	M	AML	Remission	Yes/Allogeneic	Possible	None	Lung	No
22	47	M	T-LBL	Remission	NO/NA	Probable	*Mucorales*	Lung	Yes
23	69	F	MDS	Active	NO/NA	Possible	None	Lung	No
24	20	M	BL	Remission	Yes/Autologous	Possible	None	Lung	No
25	25	F	AML	Stable	NO/NA	Probable	*Aspergillus*	Lung	Yes

Abbreviations: F, Female; M, Male; AML, Acute myeloid leukemia; DLBCL, Diffuse large B-cell lymphoma; SAA, Severe aplastic anemia; FL, Follicular lymphoma; T-LBL, T-cell lymphoblastic lymphoma; AMLL, Acute mixed lineage leukemia; MS, Myeloid sarcoma; HPS, Hemophagocytic syndrome; ANKL, Aggressive NK-cell leukemia; MDS, Myelodysplastic syndrome; BL, Burkitt s lymphoma; NA, Not applicable; IFI, Invasive fungal infection.

lymphoma (DLBCL), 2 (8.0%) patients were follicular lymphoma (FL), 2 (8.0%) patients were severe aplastic anemia (SAA), 2 (8.0%) patients were aggressive NK-cell leukemia, 2 (8.0%) patients were T-cell lymphoblastic lymphoma (T-LBL), and the other 5 patients were diagnosed as acute mixed lineage leukemia (AMLL), myeloid sarcoma (MS), hemophagocytic syndrome (HPS), aggressive NK-cell leukemia (ANKL), and Burkitt s lymphoma (BL) respectively. Twelve (48.0%) of patients received a HSCT, including 3 were autologous HSCT and 9 were allogeneic HSCT. Thirteen patients (No. 1, 4, 5, 6, 7, 11, 13, 15, 16, 17, 18, 20 and 23) were in the active phase of their primary hematologic disease, 1 patient (No. 25) was in a stable status, and the remaining were in a status of remission. Eleven (44.0%) patients had one or more co-morbidities, including cardiovascular

diseases, endocrine system diseases, digestive disorders, secondary HPS, and kidney and lung diseases. One (4.0%) patient was identified as a proven IFI with *Aspergillus*. Thirteen (48.0%) patients were categorized as probable IFI: *Aspergillus* (n = 6), *Mucorales* (n = 4), *Candida* (n = 1), simultaneous infections with *Aspergillus* and *Candida* (n = 1), and simultaneous infections with *Aspergillus* and *Mucorales* (n = 1). The remaining 11 patients were considered to have possible IFI. The key diagnostic criteria of IFI for individual patients are summarized in Table S2. Lungs infection is the common site of infection for all patients, and 4 of those patients were combined with intracalvarium (No. 3), enterocoelia (No. 7), maxillofacial region (No. 12) and gastrointestinal tract (No. 13) infection, respectively. The combined infection of fungus with any types of other pathogenic microorganisms such as bacteria and virus can be observed in 20 (80.0%) patients. Nine patients (No. 5, 7, 13, 15, 17, 19, 20, 22, and 25) presented with a clinical picture of neutropenia (defined as absolute neutrophil count ≤500 cells/mL) at the onset of IFI.

The ISZ administration-related variables are summarized in Table 2. The maintenance dosing of ISZ was 200mg once a day in all patients. ISZ was used as primary therapy in 8 cases (32.0%) and as salvage therapy in 17 cases (68.0%).

Table 2 ISZ Administration-Related Variables

Case No.	Co-antifungal with ISZ	Therapy Type of ISZ	Reason to Switch to ISZ as Salvage	Prior Antifungal Treatment	Antifungal Prophylaxis Prior to IFI	Co-Antimicrobials
1	None	Salvage	Refractory	Echinocandins	None	Antibacterial
2	Echinocandins	Salvage	Refractory	Echinocandins Voriconazole	None	Antibacterial Antiviral
3	Echinocandins	Primary	NA	None	Voriconazole	Antibacterial Antiviral
4	None	Primary	NA	None	Voriconazole	Antibacterial Antiviral
5	None	Salvage	Refractory and intolerant	Posaconazole ABCD	None	Antibacterial
6	None	Primary	NA	None	None	Antibacterial Antiviral
7	None	Salvage	Refractory and intolerant	Voriconazole Echinocandins	None	Antibacterial
8	None	Salvage	Refractory	Echinocandins	None	Antibacterial Antiviral
9	None	Salvage	Refractory and intolerant	Posaconazole ABCD	Voriconazole	Antibacterial Antiviral
10	Voriconazole	Salvage	Refractory and intolerant	Voriconazole Echinocandins LAmB	Posaconazole	Antibacterial
11	None	Salvage	Refractory	LAmB	None	Antibacterial
12	ABCD	Salvage	Refractory	LAmB	Voriconazole	Antibacterial Antiviral
13	LAmB	Salvage	Refractory	Voriconazole LAmB	Echinocandins	Antibacterial Antiviral
14	LAmB	Salvage	Refractory	ABCD Voriconazole	Posaconazole	Antibacterial

(*Continued*)

Table 2 (Continued).

Case No.	Co-antifungal with ISZ	Therapy Type of ISZ	Reason to Switch to ISZ as Salvage	Prior Antifungal Treatment	Antifungal Prophylaxis Prior to IFI	Co-Antimicrobials
15	None	Primary	NA	None	None	Antibacterial
16	None	Primary	NA	None	Voriconazole	Antibacterial Antiviral
17	None	Salvage	Refractory	Voriconazole	None	Antibacterial Antiviral
18	None	Salvage	Refractory and intolerant	Voriconazole Echinocandins	None	Antibacterial
19	ABCD/ LAmB	Salvage	Refractory	ABCD	None	Antibacterial
20	ABCD	Salvage	Refractory	ABCD Echinocandins	Posaconazole	Antibacterial Antiviral
21	None	Primary	NA	None	Voriconazole	Antibacterial Antiviral
22	ABCD	Primary	NA	None	None	Antibacterial
23	None	Salvage	Refractory	Voriconazole	None	Antibacterial Antiviral
24	ABCD	Salvage	Refractory	Posaconazole ABCD	None	Antibacterial Antiviral
25	ABCD	Primary	NA	None	Voriconazole	Antibacterial

Abbreviations: ISZ, Isavuconazole; ABCD, Amphotericin B colloidal dispersion; LAmB, liposomal amphotericin B; NA, Not applicable; IFI, invasive fungal infection.

Fourteen (56.0%) patients received ISZ alone, while 11 (44.0%) patients received it in combination with other antifungals, most commonly an amphotericin B (72.7%). The switch to ISZ as salvage therapy was driven by the refractory of primary therapy in 70.6% of cases, and refractory and intolerant of prior antifungal treatment in 29.4%.

Agents used for antifungal treatment prior to ISZ were included amphotericin B, echinocandins and triazole fungicide, but the difference in the using proportion of them was small. Anti-mold prophylaxis was used in 11 (44.0%) patients prior to the onset of infection, and the anti-mold agents were mainly voriconazole and posaconazole. One patient (No. 8) received mechanical ventilation at ISZ initiated. All patients were also applied with anti-bacterial therapy, and 14 (56.0%) patients were additionally administered with antiviral.

The treatment response to ISZ and possible ISZ-attributable adverse events are summarized in Table 3. Sixteen (64.0%) patients achieved clinical improvement and discharged. Five patients (No. 1, 3, 8, 11 and 16) died during the hospitalization. Death was attributed to infection in two patients (No. 3 and 8). Four patients (No. 7, 13, 17 and 23) did clinically aggravate

Table 3 Treatment Response to ISZ and Possible ISZ-Attributable Adverse Events

Case No.	Outcome	Causes of Death	Hepatotoxicity	Nephrotoxicity	QT Interval Changes
1	Death	Hematologic malignancy	No	No	No
2	Improvement	NA	No	No	No
3	Death	Infection	No	Yes	No
4	Improvement	NA	No	No	No

(*Continued*)

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Table 3 (Continued).

Case No.	Outcome	Causes of Death	Hepatotoxicity	Nephrotoxicity	QT Interval Changes
5	Improvement	NA	No	No	No
6	Improvement	NA	No	No	No
7	Disease aggravation	NA	No	No	No
8	Death	Infection	No	No	No
9	Improvement	NA	No	No	No
10	Improvement	NA	No	No	No
11	Death	Hematologic malignancy	Yes	Yes	No
12	Improvement	NA	No	No	No
13	Disease aggravation	NA	Yes	Yes	No
14	Improvement	NA	No	No	No
15	Improvement	NA	No	No	No
16	Death	Hematologic malignancy and HPS	Yes	No	No
17	Disease aggravation	NA	No	No	No
18	Improvement	NA	No	No	No
19	Improvement	NA	No	No	No
20	Improvement	NA	No	No	No
21	Improvement	NA	No	No	No
22	Improvement	NA	No	No	No
23	Disease aggravation	NA	No	No	No
24	Improvement	NA	No	No	No
25	Improvement	NA	No	No	No

Abbreviations: ISZ, Isavuconazole; ADR, Adverse drug reactions; NA, Not applicable; HPS, Hemophagocytic syndrome.

during ISZ treatment and discontinued treatment. Adverse events that were possibly related to ISZ were observed in only 5 patients (20.0%). Nephrotoxicity, hepatotoxicity, and blurred vision (No.7) occurred in 1 case each, and the remaining 2 cases were combined toxicity of liver and kidney.

Discussion

In this study, we detail the reasons leading to the selection of ISZ for treating IFI, and its efficacy and safety in Chinese patients with hematological diseases, which might further expand the insight of the major clinical considerations associated with the use of ISZ in a real-life setting.

ISZ is used as a primary therapy only in 8 patients in our cohort. Four patients (No. 4, 6, 16 and 21) were diagnosed with possible IFI and 4 patients (No. 3, 15, 22 and 25) were identified with *Mucorales* or *Aspergillus* infection. Though ISZ is approved for treating IA and IM, it appears viable for diagnostic-driven preemptive therapy in early IFI management, attributed to its broad-spectrum activity and favorable tolerability. Within our center, ISZ is primarily used as a salvage therapy, mostly due to refractory disease. In fact, a multicenter retrospective study conducted by Cattaneo et al demonstrated that refractoriness to other antifungal treatments did not compromise the possibility of a response to ISZ for IFI treatment, with a response rate of 70.9% for second-line treatment.[13] The response was higher

than our current cohort, in which the response rate was 58.8% (10/17) for salvage therapy. The inconsistency might be partly attributed to the heterogeneity of patients enrolled since *Aspergillus spp*. was responsible for 93% of probable/proven IFI in Cattaneo's study.[13] Notably, VITAL study has demonstrated that ISZ was efficacious as salvage therapies for mucormycosis infections, with overall end-of treatment complete and partial responses of 36%.[9] A more recent study also showed that even after the failure of other therapies, when switching to ISZ, patients had a favorable response of 40% at 6 weeks,[14] which is inferior to the results found in our study.

The intention-to-treat population analysis of the global SECURE study identified that despite higher exposure in Chinese patients, no clinically significant differences in the efficacy of ISZ were found between the Chinese and global populations cohort.[15] However, in our study, the favorable response to ISZ was 64.0% (16/25). This rate is higher than the 35% response rate reported in the SECURE trial,[8] 31% in VITAL trial,[9] and 40% observed in prior studies at 6 weeks.[14] The heterogeneity across studies may limit the comparability. But previous disparities sub-analysis showed that patients with one or more of the disparity criteria (such as age 65 years or more, obesity, diabetes mellitus, renal insufficiency, etc) had similar outcomes.[16] Therefore, a superior response rates was observed in our cohort. The all-cause mortality was 20.0% (5/25) in our center, which is higher than the previous studies in real-world use of isavuconazole.[16] The higher proportion of patients in an active status of their primary disease may contribute significantly to the elevated mortality observed at our center. Another possible reason is that the patients co-infection with SARS-COV-2 were included in our series since patients diagnosed with hematological malignancies and/or having undergone HSCT have been significantly affected by SARS-COV-2 with an initial dramatic mortality rate.[17,18] Multivariate analysis has shown that *Fusarium* infection, invasive pulmonary infection or sinus infection were the independent risk factors associated with mortality.[16] That could be another explanation for the high mortality in our study because of the lung infections is the common site of infection for all patients in our series. However, there are also studies that demonstrated the mortality rate is comparable or even higher than ours.[14,19]

Our real-life observational study showed that ISZ was well tolerated in most patients, including those with concomitant diseases such as hypertension, diabetes, renal injury etc. This aligns with previous studies that have shown that ISZ has high tolerability and a good safety profile.[13,20] Actually, SECURE and VITAL trials have demonstrated that ISZ-treated patients had a well tolerated and toxic effects compared with azoles and amphotericin B-treated groups.[8,9] This was true in particular for hepatotoxicity, nephrotoxicity and QTc-prolonging effects. On the basis of these facts, intolerance to prior therapies, especially amphotericin B intolerance, was another common indication for ISZ use as salvage therapy in our series. Notably, a unique characteristic of ISZ to shorten the QTc interval was identified in previous data,[9,21] which may allow clinicians to use ISZ in specific cases for hematologic malignancy patients and allogeneic HSCT recipients frequently require co-administration of more than one agent with potential QTc-prolonging effect (eg, macrolides, fluoroquinolones, chemotherapy agents).

In addition, 2 patients (No. 2 and 6) with the age ≥ 70 in our series also responded favorably to ISZ without untoward reactions, indicating ISZ is an effective and safe drug in the treatment of elderly patients. Our study, conducted in a hematologic setting with diverse disease types and statuses, confirms ISZ's broad applicability across various hematologic diseases at different stages of progression. As a mild-to-moderate CYP3A4 inhibitor, ISZ exhibits less pronounced drug–drug interactions. This was evidenced by our study that ISZ was well tolerated in patients undergoing HSCT who received drugs with potential cross-interaction, such as immunosuppressants. Only 11 patients received ISZ in combination with other antifungals in our cohort, mainly because prior studies have shown that there was no significant difference between ISZ monotherapy and combination therapy.[14] Ten patients received azole prophylaxis in our center and 8 of them had a favorable response to ISZ, suggesting ISZ is an excellent candidate for breakthrough fungal infections in patients who had taken azole for prophylaxis.

This study has limitations, including its retrospective design, small sample size, limited follow-up duration, and single-center scope. Moreover, only a few patients received ISZ as primary treatment and only one proven IFI case was included further limited our study. Therefore, the findings of our study should be extrapolated with caution and further studies are warranted to confirm these data.

Conclusion

In conclusion, although wider applicability of our results cannot be assumed, our findings lead to a speculation that whether used as primary or salvage therapy after the failure or intolerance of other prophylaxis or therapies, ISZ seems to have a promising clinical response and a good safety profile for treating IFI in Chinese patients with hematologic diseases.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Disclosure

The authors declare no conflicts of interest in this work.

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